

# **CUTANEOUS MALIGNANT MELANOMA**

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**M D THESIS**

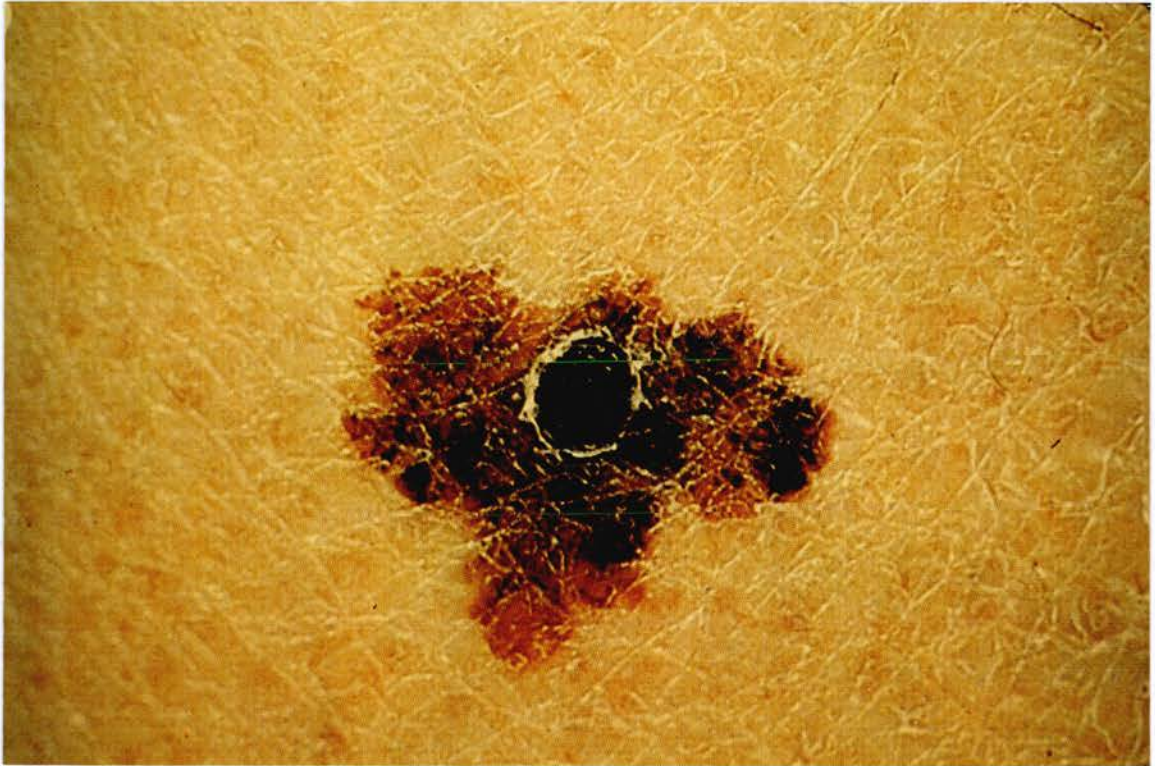
**UNIVERSITY OF EDINBURGH**

**1991**



**Figure 1.**

**Superficial spreading malignant melanoma**



Legend : the superficial radial component is seen surrounding the invasive nodule.



# **ACKNOWLEDGEMENTS AND DECLARATION**

I wish to express my sincere thanks to the following for help in various aspects of this thesis :

1. The British Columbia Cancer Agency [BCCA].
2. Health Records Departments of the Victoria and Vancouver Clinics of the BCCA.
3. The Melanoma Tumor Group of the BCCA.
4. Dr A Worth, Head of Anatomic Pathology, BCCA for review of histopathology.
5. Ms V Carmichael BSc, Faculty of Health Information Science, University of Victoria for assistance in data base management and statistical analysis.
6. The British Columbia Cancer Foundation for medical student summer project grants : Dr D Lister and Dr S Ashwell assisted with review of medical records.
7. Mr R Gallagher and Mr J Spinelli, Division of Epidemiology, BCCA for consultation and advice.

8. Professor J A A Hunter, Department of Dermatology, University of Edinburgh, adviser for this thesis.

9. Mr P Anglin, post-graduate student at Victoria Clinic, for introduction to personal computing and word-processing.

10. The manuscript was prepared by Dr K S Wilson utilising ATARI 1040ST personal computer with First Word Plus and LDW Power Spreadsheet software, and thesis submitted August 1991. The manuscript was amended by Dr K S Wilson after viva voce examination, October 26, 1993, in Edinburgh. Compaq Contura 386 with Word Perfect for Windows and Quattro Pro software. Three reprints from published papers submitted to the Examiners after initial thesis submission are included in this final bound thesis.

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## ABSTRACT

Epidemiology, clinical presentation, natural history, pathological features and treatment of cutaneous malignant melanoma have been studied in the British Columbia Cancer Agency [BCCA]. A retrospective review of 891 patients registered between 1972 and 1981 is presented.

Age standardised incidence rates have increased significantly. Incidence rates in males and females in 1988 were 11.5 and 12.8 per 100,000 respectively. Sex ratio was 1.13 : 1 in favor of females and median age was 47 years. Change in size of a mole was the commonest presenting symptom and median symptom duration before primary treatment was 5.9 months. Predominant primary sites were trunk for males and lower limb for females.

Dominant growth patterns were superficial spreading melanoma [65%], nodular melanoma [25%], lentigo maligna melanoma [5%] and acral-lentiginous melanoma [2%]. Staging of the primary tumor was local [90%], regional [9%] and distant [1%] at presentation. Median primary tumor depths at presentation were 1.45mm for males and 1.10mm for females. No T1 tumors were staged beyond the local area.

Disease recurred in 44% of males and 32% of females. Fifteen year survival was 55.5% for males and 70.3% for females. These findings compare favorably with other recent world experience.

Of the whole series, 753 patients with clinical stage 1 disease were identified and 28 clinical and pathological variables were subjected to prognostic factor analysis. Univariate analysis showed the following factors to be significant in descending order : Clark level, depth, clinical and pathological ulceration, growth pattern, tumor volume, sex, date of diagnosis, surface description, lymphatic invasion and primary site [all  $p < 0.0001$ ], inflammatory reaction, BANS sites, pigmentation, mitotic rate, polypoid configuration, invasion to stratum corneum, tumor diameter [all  $p < 0.0052$ ], and type of surgery [ $p = 0.0472$ ]. Primary color was marginally significant, but cell type, type of inflammatory infiltrate, age, clinical and pathological regression, type of regression, and history of previous nevi were insignificant.

Multivariate analyses of prognostic factors in 556 patients showed that micrometer depth, pathological ulceration, primary site and type of initial surgery were the principal prognostic factors. An alternate model coding primary sites differently showed BANS [upper back, posterior upper arm, neck and scalp] sites and sex to be significant while other primary



sites ceased to be significant : adjusting this model for Clark level made BANS sites and sex again significant along with lymphatic invasion. Using linear coding for categorical variables, the following covariates were significant : depth, primary site, pathological ulceration, type of surgery, growth pattern, Clark level, BANS sites and lymphatic invasion [in descending order]. Significant factors after depth adjustment was made were [in descending order] Clark level, ulceration, BANS sites, type of surgery, sex and lymphatic invasion. The significant factors in multivariate analysis have been compared with the results of 60 other reports worldwide. The present report confirms primary site, depth and pathological ulceration as key prognostic factors. Inter-relations between several prognostic factors, notably depth, diameter, age, sex, primary site, growth pattern, ulceration and mitotic rate contribute to the reported variation in prognostic significance attached to these covariates.

Elective lymph node dissections were undertaken in 232 patients, 208 of whom had primary depth measured. Nodes examined after elective lymph node dissection were positive pathologically in 36 [16%] patients, 18 with 1, 7 with 2, 8 with 3+ and 3 with unspecified number of nodes positive. Ranges and median depths of primary in patients with positive and negative elective dissections were 0.85 - 8.00mm and 3.00mm, and 0.45 - 7.00mm and 1.6mm respectively.

Positive/negative elective dissection ratios were : 20/86 and 16/102 in males and females : 3/42 [upper limb], 16/76 [lower limb], 12/45 [trunk], 5/24 [head and neck] : 16/103 [superficial spreading melanoma], 15/57 [nodular melanoma], 0/3 [acral-lentiginous melanoma] : 5/68 T2 primary, 12/66 T3, 14/20 T4 : 3/64 Clark level III, 25/106 level IV and 6/8 level V. Disease recurred in 23 [64%] elective node dissection positive and 47 [25%] negative patients with corresponding median survivals of 4.2 and 9.1 years.

In spite of having thicker primary tumors [median depth 1.7mm] ELND patients had superior survival compared with Control patients [median depth 1.00mm]. The survival differences were principally in T2 and Clark level IV primaries. However, the Control group had more unfavorable primary sites.

Ten year disease-specific survival for all patients undergoing wide primary excision [ $>5$ cm total width of specimen] and ELND for clinical stage 1 melanoma was 67%. Over the same period, 10 year survival for clinical stage 1 patients having only wide excision was 67%. Multivariate analysis of potential prognostic factors did not show ELND to be of independent significance in clinical stage 1 patients.

Survival comparisons were also made with extremity primary patients treated with ELND in the World Health Organisation prospectively randomised study. BCCA ELND patients had better survival in all groups examined, likely due to more favorable primary depths. Further comparisons were made in the subgroups of T3 primary patients : male, trunk : male, extremity : female, extremity. Survival of BCCA ELND and Control patients was compared with results from the University of Sydney in these subgroups. BCCA survival results were intermediate between the Sydney control and ELND groups and did not show any advantage for ELND.

Therapeutic node dissections were performed in 50 patients and 36 [72%] were positive. Range and median depths of primaries in patients with positive therapeutic node dissections were 1.67-8.00mm and 2.00mm respectively. Disease recurred in 24 [67%] positive therapeutic node dissection patients with median survival 2.7 years.

Therapeutic lymph node dissections were also performed in 90 patients with regional node metastases from previous primary melanoma. Range and median depth of responsible primaries were 1.0 - 7.0mm and 2.0mm respectively. Median time to regional lymph node recurrence from primary treatment was 1.5 years. Median survival was 1.8 years from the



date of regional node recurrence, and 4.4 years from primary diagnosis. Median survivals of ELND negative, positive and TLND patients compare favorably with reports from New York, Chicago and Buffalo.

Survival comparisons were also made between all 3 groups of BCCA lymph node dissection positive patients ie ELND +ve, TLND +ve and RTLND. Survival was defined from the date of LND positive surgery. No statistically significant difference in survival was demonstrated.

## **CHAPTER 1**

# INTRODUCTION

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5. Depth assessment.
6. World Health Organisation contributions.
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## **1. Incidence of malignant melanoma.**

Malignant melanoma represented 3.1% and 3.7% of cancers in males and females in British Columbia in 1987 [Gallagher and McBride, 1987]. The present incidence of 11.5 and 12.8 per 100,000 for males and females has more than doubled since the 1970's. However, translated into the likelihood of individual general physicians encountering melanoma, the probability of a physician caring for 1000 patients annually seeing a new melanoma patient is remote. In 40 years of general practice one would expect to see about 4 or 5 new melanoma patients, or one every 8 years on average. Many patients have excision biopsies before they are seen by consultants in North America. Practical experience among junior physicians and medical students of seeing primary melanoma or indeed patients with relapse is limited. Individual physicians and their patients, on whom early diagnosis depends, must be alert to the possibility of melanoma [Kopf, 1988 : Mackie 1990].

## **2. Historical Perspective**

The history of malignant melanoma has been divided into three periods [Veronesi, 1985]. The original description of partly black metastatic tumor in cervical lymph nodes by Dr John Hunter in 1787 was later confirmed histologically as melanoma [Bodenham, 1968]. Malignant melanoma has however existed for centuries. Gross and histological

evidence of melanoma has been found in nine mummies of pre-Columbian Incas from Peru [Urteaga and Pack, 1966]. These bodies are estimated to have lived over 2400 years ago. The term "melanosis" was applied to black tumor deposits in visceral organs [Laennec, 1812]. The first English language report of cutaneous malignant melanoma was an anterior abdominal wall primary in a middle-aged male who developed local, regional and distant metastases [Norris, 1820]. Interestingly, the patient's father had died from metastatic melanoma. The associations of melanoma arising in a pre-existing mole and in individuals with fair hair and complexion were also established. The now-familiar patterns of metastatic disease were described and wide excision was advocated to prevent local recurrence.

Observations of growth in diameter followed by growth in height in a primary melanoma [Williams, 1834 reported by Silvers, 1982] may have been the first description of what are now described as the radial and vertical growth phases. Primary sites in the nail bed [sub-ungual] and face were recognised later [Hutchinson, 1857 & 1892].

Therapeutic lymphadenectomy for recurrence was first reported in 1851 [Case Report, 1851]. Recommendation for elective lymph node dissection [Snow, 1892] marks the beginning of the second period of

melanoma history. This concept, along with wide excision of the primary site, was affirmed following the demonstration at autopsy of lymphatic permeation in a patient dying from melanoma [Handley, 1907]. Wide primary excisions and regional lymph node dissections were widely practiced thereafter until the 1970's.

The third and contemporary period started with the constitution of the World Health Organisation [WHO] International Melanoma Group, the establishment of a geographic multi-disciplinary study in Queensland, Australia [Davis, Mcleod, Beardmore et al., 1976], and new definitions of histopathology of melanoma, describing growth patterns and depth of invasion. To these developments in the past 25 years, the most recent areas of progress should be added. These include the recognition of the dysplastic nevus syndrome and its relation to familial and sporadic melanoma, contemporary knowledge of the complexities of the immune system, advances in bio-technology including genetic engineering and monoclonal antibodies, chromosome abnormalities and oncogene expression in dysplastic nevi and melanoma, and the availability of new cytokines in the treatment of malignant melanoma [Yarbro, 1988].



### **3. Contemporary philosophy of melanoma etiology, pathology and treatment.**

Prior to 1969 there was a widespread assumption that malignant melanoma invariably arose in melanocytic nevi [Clark, From, Bernardino et al., 1969]. Nevi are classified [Roses, Harris, Ackerman, 1983] as congenital or acquired, according to location of the nevus cells [epidermis/junctional ; dermis/intradermal ; epidermis + dermis/compound], and according to the cell type [eg Spitz nevus/large spindle +/- balloon cells ; blue nevus/ melanocytes dendritic or spindle-shaped or both]. The description of intradermal portions of malignant melanoma discrete from the invasive component was in contrast with previous interpretations of co-existing "junctional activity" ie benign nevus [Clark, Ainsworth, Bernardino et al., 1969]. Evidence of a pre-existing benign nevus was considered present in only 8.3% of melanomas.

### **4. Growth Patterns.**

Three types of melanoma according to histologic criteria have been described. The invasive component was defined in terms of anatomic depth and the latter related to risk of recurrence and death from melanoma. Classification was based on the appearance of the non-invasive component since the invasive parts are indistinguishable [Clark, Ainsworth, Bernardino et al., 1969 ].

**Superficial spreading melanoma [SSM]** and **lentigo maligna melanoma [LMM]** by definition have a radial growth component beyond the width of at least 3 rete ridges beside the invasive nodule in any section, while the invasive component of **nodular melanoma [NM]** has a negligible adjacent component. The superficial spreading part of SSM is described as the radial growth phase. SSM and LMM are distinguished on morphologic grounds, SSM for example usually having epithelioid cells of uniform appearance. LMM occurs mainly on the head and neck, has an irregular outline, mainly flat surface, and primarily shades of brown in color. SSM has haphazard colors, sharp demarcation of outline, and irregularly elevated surface. NM is uniformly invasive, raised to variable degree, sometimes exophytic and ulcerated. Complete clinical and pathological descriptions of primary melanoma are widely available [Davis, McLeod, Beardmore et al., 1976]. Representative clinical photographs of SSM, LMM and NM are shown in Figures 1, 2 and 3.

A fourth histogenic or growth pattern of primary melanoma arising on the palms, soles or nail-beds was named **acral-lentiginous melanoma [ALM, Figure 4]** [Reed, 1976]. This is the same clinico-pathological entity as the original "melanotic whitlow" [Hutchinson, 1886]. This type of melanoma is also characterised by a radial growth phase, in which there is acanthosis, elongation of rete ridges and lentiginous proliferation of

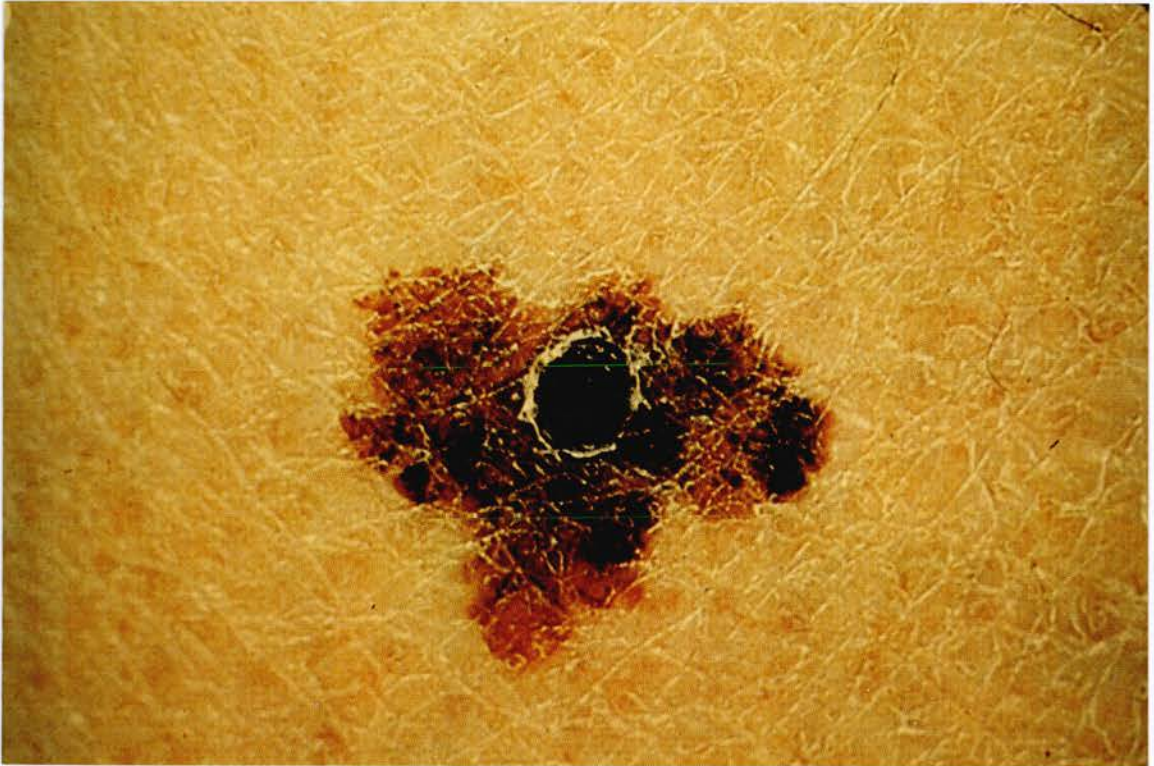
atypical melanocytes in the epidermis. Similarities between the radial phases of ALM and mucosal membrane melanomas have led to a recommendation that they be classed together [Clark, Bernardino, Reed et al., 1979].

## **5. Depth Assessment.**

Depth of invasion is classified in 5 anatomic levels, shown diagrammatically in Figure 5. In level I, all tumor cells are superficial to the basement membrane ie in situ. In level II, tumor cells penetrate the basement membrane into the upper part of the papillary dermis. In level III, tumor cells extend to the interface of papillary and reticular dermis. In level IV, tumor cells extend into the reticular dermis. In level V, tumor cells invade subcutaneous tissue.

**Figure 1.**

**Superficial spreading malignant melanoma**



Legend : the superficial radial component is seen surrounding the invasive nodule.



**Figure 2.**

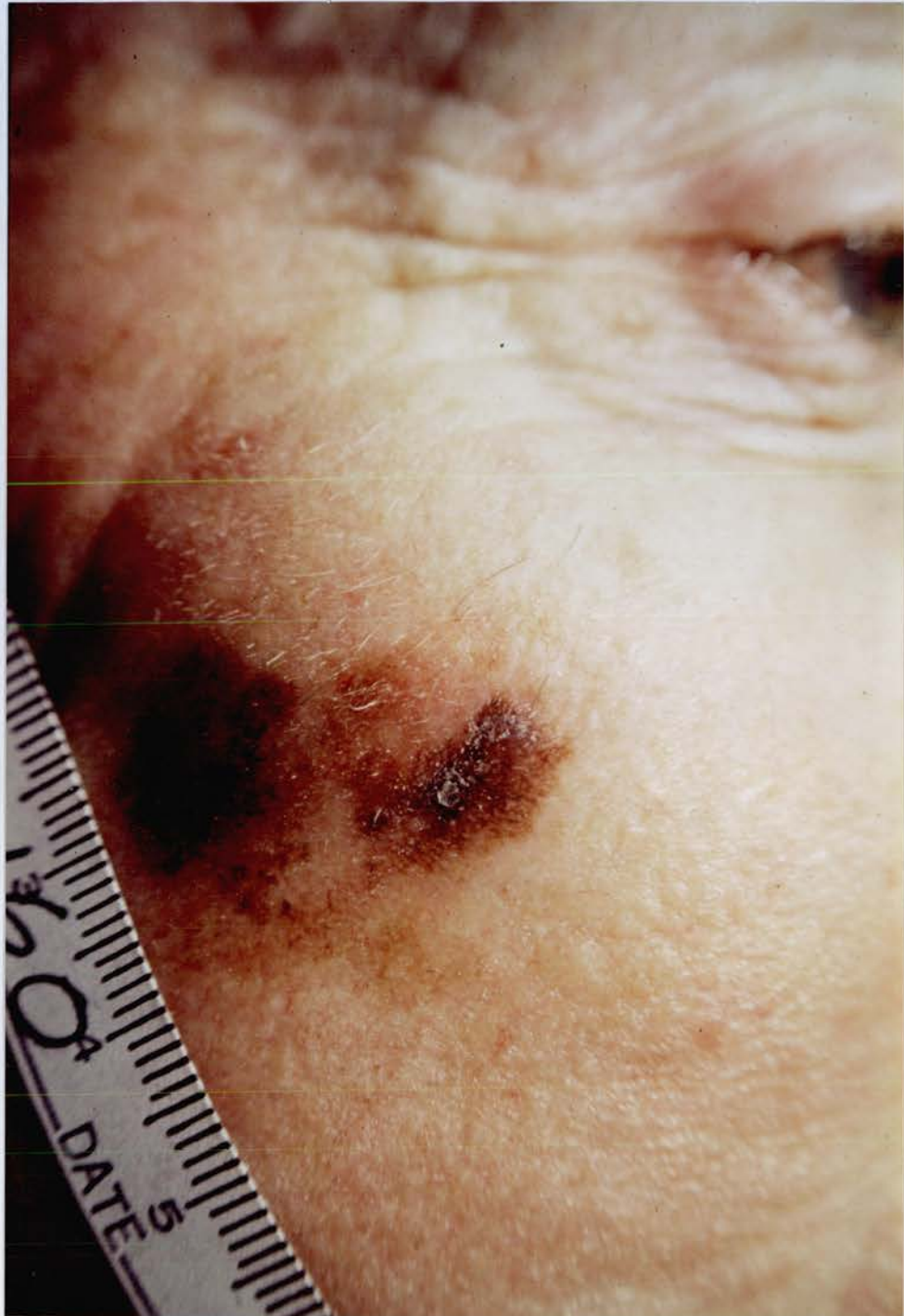
**Nodular malignant melanoma**



Legend : no radial component adjacent to the invasive nodule is noted.

**Figure 3.**

**Lentigo maligna melanoma**





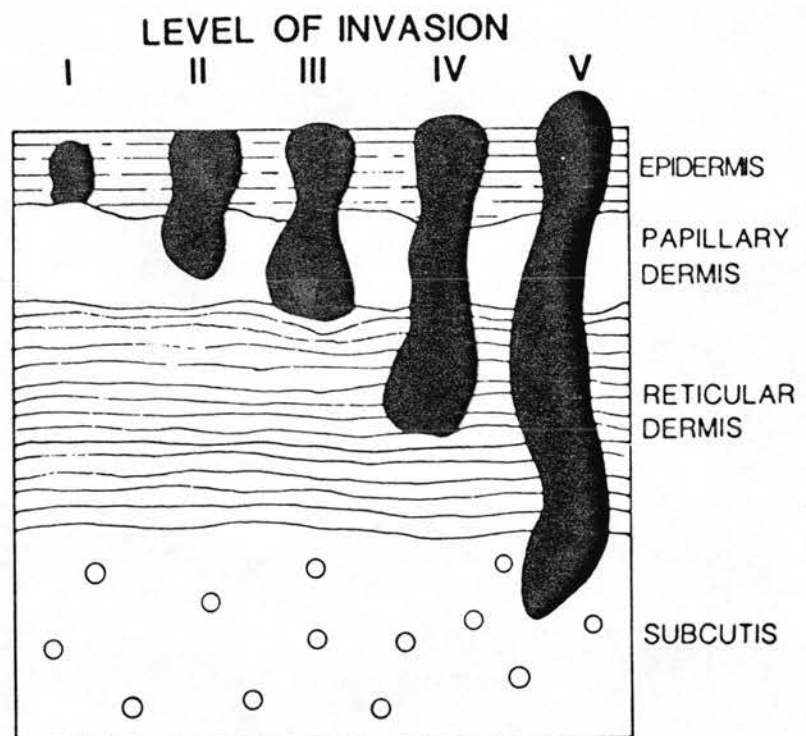
**Figure 4.**

**Acral lentiginous malignant melanoma**



**Figure 5.**

**Clark levels of invasion**



In addition to anatomic depth, tumor thickness has also been measured by micrometer [Breslow, 1970]. Vertical measurement of tumor thickness from the upper level of the granular layer of the epidermis to the deepest part of the tumor has been found to be the best single indicator of prognosis [Breslow, 1970 : Balch, Murad, Soong et al., 1978 : McGovern, Shaw, Milton, 1979]. Many groups and institutions have since reviewed their experience of malignant melanoma using the above criteria for growth pattern and depth of invasion. These are discussed along with British Columbia Cancer Agency [BCCA] experience in Chapter 2.

## **6. World Health Organisation contributions.**

The World Health Organisation [WHO] Melanoma Group has made significant contributions in the assessment of treatments for melanoma. The importance of prospective randomised trials for new and indeed some time-honored treatments has been realised. The WHO Group has conducted a study in patients with melanomas less than 2 mm thick and found no advantage to a 3 cm width of excision compared with 1 cm [Veronesi, Cascinelli, Adamus et al., 1988]. The trend towards narrower excision margins for melanoma is supported by this study. A representative example of a wide excision around a primary melanoma of the posterior trunk is shown in Figure 6 ; fewer procedures of this type are being performed as a result of clinical trials of surgical margins. The WHO

Melanoma Group has also conducted a prospective randomised study of elective lymph node dissection [ELND] in extremity melanoma [Veronesi, Adamus, Bandiera et al., 1982] which did not confirm the beneficial expectations from non-randomised studies and has led to a further on-going study of ELND in patients with trunk primaries over 2 mm thick. They also conducted a study of adjuvant chemotherapy and immunotherapy which showed no benefit from either [Veronesi, Adamus, Aubert et al., 1982].

## **7. Genetics and Family Studies including Dysplastic Nevus Syndrome.**

Genetic studies of malignant melanoma have attempted to identify genes involved in the transformation of melanocytes and in melanoma tumor progression [Drapacoli and Bale, 1988]. Methodologies include : screening melanoma cells for dominant acting oncogenes, screening for recessive tumor genes by loss of heterozygosity analysis of matched sets of DNAs from melanoma and normal lymphocyte samples, genetic linkage studies of familial melanoma and dysplastic nevus syndrome.

**Figure 6.**

**Wide Excision : Primary Melanoma of Posterior Trunk**





No consistent oncogene activation has yet been observed. Cytogenetic abnormalities of chromosomes 1, 6 and 7 have been reported [Balaban, Herlyn, Clark et al., 1988] but without associated oncogene changes. There is presently no strong evidence implicating loss of heterozygosity in the transformation of human melanocytes.

Studies of patients with positive family histories of malignant melanoma led to the identification of a precursor to melanoma, the "**dysplastic nevus**" [Clark, Reimer, Greene et al., 1978 ; Figure 7]. Such nevi have characteristics which are different from normal acquired nevi [Greene, Clark, Tucker et al., 1985]. They are often larger than 5mm diameter and usually have a macular component. A central papular area may give a "fried egg appearance". Borders are irregular and indistinct. Colors therein are variable from pink to dark brown. They are most frequent on sun-exposed areas but also occur on less sun-exposed areas. The number of dysplastic nevi is directly related to the amount of sun exposure [Kopf, Lindsay, Rogers et al., 1985]. They are usually absent at birth and may be associated with a normal nevus distribution or an excess of morphologically normal nevi. They are often not apparent until puberty and continue to appear throughout adult life. Histologically, they are distinctive with melanocytic hyperplasia of large epithelioid melanocytes with variable nuclear atypia in the basal layers, a patchy lymphocytic



infiltrate, concentric eosinophilic fibroplasia and lamellar fibroplasia. In dysplastic nevi positive family members of patients with melanoma, the relative risk of melanoma is 150-fold increased above normal [Greene, Clark, Tucker et al., 1985], those with the largest number of nevi being at the greatest risk [Kraemer, Greene, 1985]. Familial melanoma is transmitted as an autosomal dominant and this has implications for surveillance of first degree relatives [Drapacoli and Bale, 1988].

Dysplastic nevi also occur in the general population, with an estimated prevalence between 5-8% [Rhodes, Sober, Mihm et al., 1980 : Crutcher and Sagabiel, 1984 : Holly, Kelly, Shpall et al., 1987]. Recent studies associating melanoma incidence and presence of nevi have distinguished normal from dysplastic nevi. Increased melanoma risk has been attributed to both the presence of dysplastic nevi [Holly, Kelly, Schpall et al., 1987 : Roush, McKay, Forget et al., 1986] and benign melanocytic nevi [Swerdlow, English, Mackie et al., 1986]. The risk of melanoma in sporadic dysplastic nevus syndrome patients has been estimated at 10 times normal [Kraemer, Tucker, Tarone et al., 1986]. Fibroblasts and lymphoblastoid cells from familial melanoma and dysplastic nevi patients exhibit increased sensitivity to ultraviolet radiation and increased mutagenesis respectively [Smith, Greene, Devlin et al., 1982 : Perera, Um, Greene et al., 1986].

## **8. Other Risk Factors for Melanoma.**

Other risk factors for the development of malignant melanoma have been investigated mostly by retrospective analysis or case - control studies. Sun exposure has been implicated in the pathogenesis of malignant melanoma for several reasons ; there is an inverse relationship between melanoma incidence and latitude : there is a difference in melanoma incidence according to skin type, being lowest in blacks and highest in whites : there is a higher incidence of melanoma on the trunk in men and lower extremity in females, suggesting that clothing may be protective [Loggie and Eddy, 1988].

Relative risks of developing malignant melanoma have been calculated for 10 factors [Rhodes, Weinstock, Fitzpatrick et al., 1987]. These are summarised, along with relative risk factors, overleaf. However, all these factors except change in mole size or color collectively can account for only about half the cases of malignant melanoma. The observations that the incidence of melanomas of the head and neck in older patients is increasing slowly while the incidence of those on the trunk is increasing rapidly and occurring in younger patients suggest that as yet unknown events of youth are implicated in the pathogenesis of melanoma [Lee, 1990]. For the present, physicians and patients must focus on primary prevention against the known risk factors, and secondary

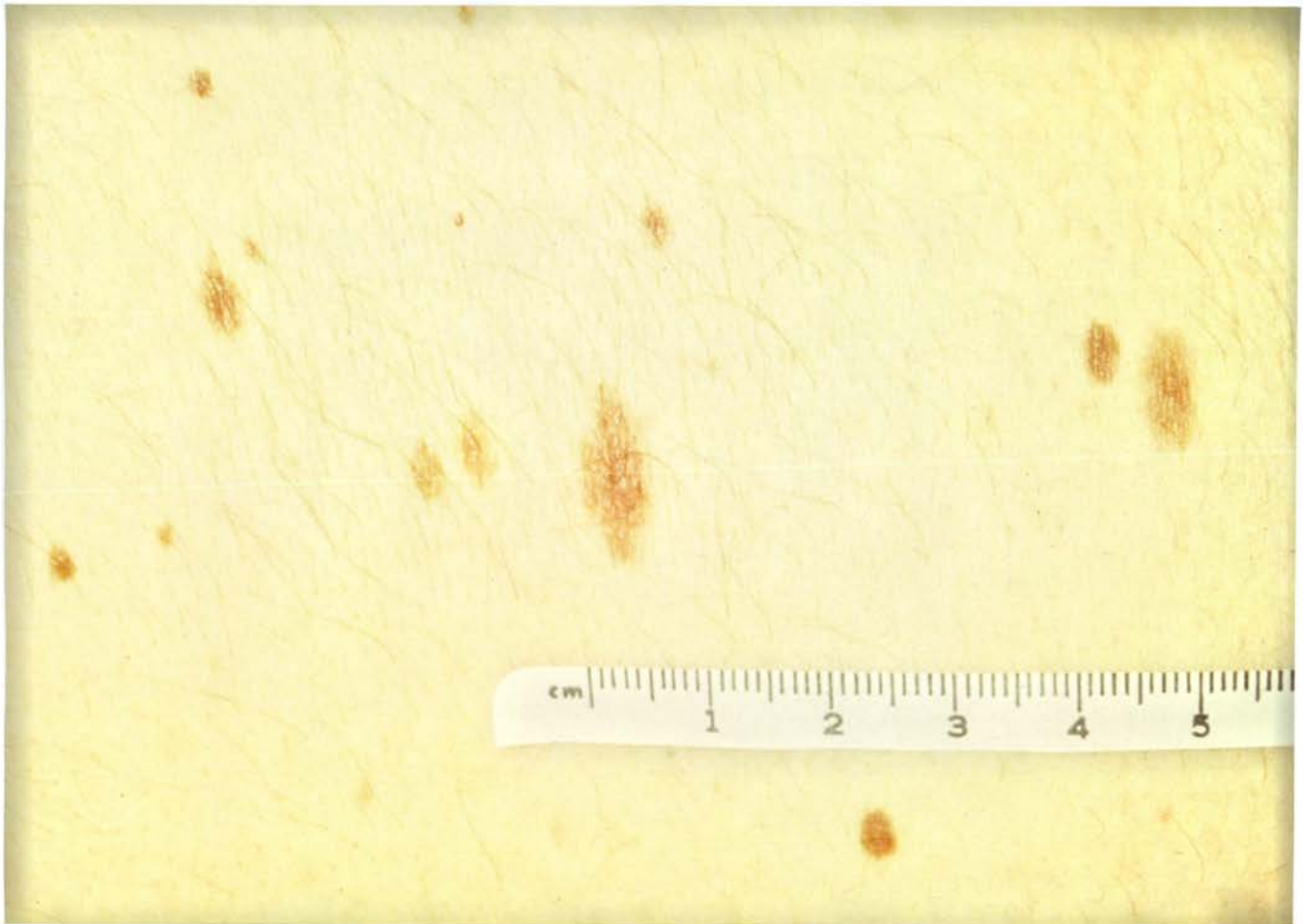
prevention ie early detection and treatment [Rhodes, Sober, Mihm et al., 1987 : Mackie, Freudenberger, Aitchison, 1989].

## Relative risks of developing malignant melanoma

	Relative Risk
Persistently changed or changing mole	>400
Age > 15 years vs < 15	88
<b><i>1 + large or irregularly pigmented lesions:</i></b>	
Dysplastic mole and familial melanoma	148
Dysplastic mole without " "	27
Lentigo maligna	10
Congenital mole	21
Caucasian race	12
Previous melanoma	9
Family history of melanoma	8
Immunosuppression	4
Sun sensitivity	3
Excessive sun exposure	3

**Figure 7.**

**Dysplastic nevus**



## **9. Adjuvant Therapy.**

Surgery and radical radiation therapy have significant failure rates in the common solid tumors. The concept of adjuvant therapy, treatment aimed at eradicating microscopic metastases in patients in whom all visible disease has been removed, has been investigated in many solid tumors and has become standard practice in several eg stage 2 breast cancer [Bonnadonna, 1989].

Treatment selected for investigation as adjuvant therapy should be able to produce some complete remissions in advanced metastatic disease in humans or prevent recurrence in animal tumor systems after primary surgery. Even if partial responses are the best response category seen in advanced disease, there are kinetic reasons to expect that the same treatment may still be able to prevent recurrence.

After a potential adjuvant therapy has been developed, the appropriate patient population to whom it may be offered is identified. The expected prognosis of patients who have had initial definitive therapy is assessed. Usually patients with at least a 25% chance of recurrence are considered for adjuvant therapy studies. The risks/toxicities of the proposed adjuvant therapy must also be considered [Salmon, 1986]. In melanoma, many trials of immunotherapy and chemotherapy or both combined have

been undertaken [Balch and Hersey, 1985].

Patients with malignant melanoma who are at significant risk of recurrence can now be identified. The principal risk factor in the primary is depth, and any patient who has had a recurrence is at extreme risk of further recurrence and death.

Chemotherapy for advanced melanoma rarely produces complete remissions. Partial remissions are the rule and the response rate is only 20-25% [Balch, Milton, 1985]. Adjuvant chemotherapy studies have not shown any reduction in mortality in either stage 1 high risk or lymph node positive melanoma [ Balch, Hersey, 1985].

The relation between host [patient] and tumor [melanoma] has fascinated physicians for decades. Observations of spontaneous regression in primary and metastatic melanoma, and the phenomenon of late recurrence many years after primary treatment pointed to a relationship which might be exploited to the patient's advantage. This is the basis of adjuvant immunotherapy, administration of drugs or biological materials to restore or enhance the ability of the patient's immune system to recognise and destroy micrometastases.



The selection of agents for development as immunotherapy does not follow the same guidelines as for chemotherapy. Immunotherapy agents are not expected to be able to eradicate large tumor masses. Ideally certain host defence mechanisms can be quantitated and the immunomodulatory effect of drugs or biological materials assessed thereafter. In the 1970's, few tests of immune function were available. Tuberculin testing was the only routine test for cellular immunity. Even in the late 1980's, while T lymphocyte function tests and immunomodulatory doses of interferon could be selected in the laboratory [Maluish, Walter, Urba et al., 1988], their effects in vivo in clinical trial in melanoma have not shown any benefit [Meyskens, Kopecky, Samson et al., 1991]. In the 1970's, several approaches to boost host defences were taken including Bacillus Calmette-Guerin [BCG], *Corynebacterium parvum* and levamisole.

**BCG** was introduced as a non-specific immune system stimulant [Bast, Zbar, Borsos et al., 1974 : Lamoreux and Turcotte, 1976]. BCG acts as a potent non-specific stimulator of macrophages and the reticulo-endothelial system. In animal tumor systems, prophylactic BCG immunisation will suppress the development of some transplanted antigenic tumors and can cause the regression of established cancers in experimental tumor models. Established skin tumors regress after intralesional BCG. Survival is enhanced if BCG is given after surgery for

spontaneous mammary cancer in rats.

**Levamisole**, initially introduced as an antihelminthic in 1968, was found to increase immunity to Brucella infection in mice [Renoux and Renoux, 1971] and subsequently shown to restore several T cell functions and phagocytic functions in polymorphonuclear cells, monocytes and macrophages. It did not, however, enhance normal immune functions [Amery and Horig, 1984]. Dinitrochlorobenzene [DNCB] reactivity in anergic cancer patients was restored after levamisole administration [Tripodi, Parks, Brugmans, 1973]. Levamisole was investigated in a randomised trial [Spitler and Sagabiel, 1980] in the 1970's in melanoma and there was a trend towards improved survival [ $p = 0.07$ ] in levamisole-treated patients.

From 1979-82, the National Cancer Institute of Canada Clinical Trials Group Melanoma Committee undertook an adjuvant trial of BCG and levamisole [Quirt, Shelley, Bodurtha et al, 1986]. Prior to the activation of this trial, BCG was recommended routinely to high risk melanoma patients in British Columbia although at that time there was conflicting evidence of benefit [Silver, Ibrahim, Evers et al., 1983]. A prospective randomised trial including BCG was thought appropriate and duly commenced as a multi-centre study. Results of this study showed a reduction in melanoma mortality by 30% in patients receiving levamisole, but no benefits from

BCG [Quirt, Shelley, Pater et al., 1991]. I entered and treated 41 patients in this co-operative study.

A second NCIC adjuvant trial comparing levamisole with gamma interferon was commenced in 1988 but accrual was terminated in 1990 because a study from the South West Oncology Group failed to show any suggestion of the anticipated benefit from gamma interferon [Meyskens, Kopecky, Samson et al., 1991]. This latter study compared gamma interferon with observation as adjuvant therapy in completely resected stage 1 melanoma > 1.5 mm thick.

## **10. Chemotherapy.**

From a chemotherapy viewpoint, malignant melanoma presents many problems, being one of the least sensitive tumor types to conventional anti-cancer drugs [Balch, Houghton, Peters, 1989]. This has led to a focus on new drug development in the laboratory and clinic. There has, however, been little progress in this direction over the past 20 years since the introduction of imidazole carboxamide [DTIC]. Virtually every new potential anti-cancer drug is evaluated first in refractory tumors such as metastatic melanoma, non- small cell lung cancer and renal cell carcinoma [de Vita, 1989]. Medical oncology literature abounds with negative reports of activity of new drugs in malignant melanoma [Rumke, 1986 ; Rumke,

1988 ; Smyth, 1990]. Drugs which have produced "responses" in metastatic melanoma rarely cause complete tumor regression and improvements which do occur are usually short-lived. The same principles which led to the development of successful chemotherapy in malignant lymphomas have been adopted in melanoma, but simultaneous use of drugs with different mechanisms of action and non-overlapping toxicities have failed to provide the desired quantum leap forward.

The Melanoma Group of the National Cancer Institute of Canada has participated in this search with drug combinations of cis-platinum, vinblastine and bleomycin [NCIC Melanoma Group, 1984], and vincristine, procarbazine and CCNU [Shelley, Quirt, Bodurtha et al., 1985]. The Melanoma Tumor Group of the BCCA has also undertaken a phase 2 study in melanoma with dibromodulcitol [Murray, Silver, Shah et al., 1985]. I was involved as a local investigator treating patients with these regimens. Publications on these subjects are attached in the Appendix.

Regional administration of chemotherapeutic agents has been investigated in patients with local-regional recurrence or who are at high risk thereof. This technique has been combined with regional hyperthermia to try to increase the therapeutic index [Krementz, Ryan, Carter, 1985]. A recent randomised trial of hyperthermic perfusion with L-phenyl alanine

mustard [melphalan] showed a reduction in recurrence rate among resected high risk stage 1-3 patients [Ghussen, Kruger, Groth et al., 1987]. This technology is not however widely available. No hyperthermia facilities are available in British Columbia and regional chemotherapy perfusion is rarely undertaken.

## **11. Biological Therapy.**

Biological treatments as potential adjuvant therapy and for advanced disease have been under intensive investigation in the 1980's. Expanding knowledge of the complexities of the immune system and genetic engineering technology have combined to permit study of newly discovered cytokines, monoclonal antibodies and hemopoietic growth factors [de Vita and Roper, 1987]. Vaccines with melanoma-associated antigens have been developed and tested in advanced disease and as adjuvant therapy [Rumke, 1988]. Vaccines combining tumor cells and viruses [eg vaccinia, Newcastle disease virus] to enhance immunogenicity of the tumor cells have been tested in phase 1 and 2 adjuvant studies [Wallack, Bash, Bartolucci, 1989].

**Interferon** was discovered [Isaacs and Lindemann, 1957] while studying the phenomenon of viral interference [cellular resistance induced by a virus to superinfection by another virus]. The inhibition of growth of



uninfected mouse cells in culture was the first demonstration of the anti-proliferative of interferon [Paucker, Cantell, Henle, 1962]. Subsequently, several species of interferon have been recognised. The original interferon was beta interferon. Alpha interferon derived from Burkitt's lymphoma [lymphoblastoid] or prepared by recombinant DNA technology [alpha-2a, 2b and 2c] has been tested extensively in metastatic melanoma. Alpha interferons share the same receptor and clinical anti-cancer activities. Anti-tumor activity may be expressed by direct effects on tumor cells and also by indirect immune stimulation. Gamma interferon, or immune interferon, has some unique properties, increasing expression of Class II histocompatibility antigens and producing greater macrophage stimulation [Silver, 1986]. Although much is known about the biological effects of interferon, the explanation for the exquisite sensitivity of hairy cell leukemia cells to "minimal" doses of alpha interferon remains a mystery. Similarly, the relative resistance of many tumor types, including melanoma, to massive doses of interferon is poorly understood.

Interferon [alpha and gamma] has been tested in patients with metastatic melanoma using several different doses, schedules and routes of administration [Silver, 1986]. From these studies, it can be concluded that some patients exhibit tumor shrinkage, that best responses may take several months, that stabilisation may be a more worthwhile response



category with biological agents as opposed to chemotherapy, that dose / response relationships may be more complex than with chemotherapy agents, and that in vitro correlates of activity are required for further clarification of optimal dose and schedule. Interferon has also been administered directly into metastases of melanoma with local tumor regression in 24 of 26 patients ; 9 patients also had responses in distant sites [von Wussow, Block, Hartmann et al., 1988]. Combination therapies eg interferon alpha and gamma, interferon and interleukin, interferon and tumor necrosis factor, interferon and chemotherapy are also being investigated in metastatic melanoma. Although the mechanisms of action may be different and theoretically additive therapeutic effects might be expected, there is certainly potential for additive toxicities, notably hematologic and constitutional. Such combination therapies are presently in phase 1 and 2 development stages [Hirsh, Lipton, Harvey et al., 1990 : McLeod, Thompson, Hersey, 1987].

Initial dramatic results of **interleukin 2** and **lymphokine-activated killer [LAK] cell therapy** for metastatic melanoma at the United States National Cancer Institute [Rosenberg, Lotze, Muul et al., 1985] have unfortunately not been confirmed by subsequent extramural studies of the same agents given in the same manner [Dutcher, Creekmore, Weiss et al., 1989]. In any event, the toxicities of interleukin 2 were so severe that many

patients required intensive care unit support. Clearly, the practicalities of its administration would have been prohibitive for most hospitals. The necessity for LAK cells in producing responses with interleukin has been questioned since interleukin alone has been shown to produce a similar response rate in metastatic melanoma [Parkinson, Abrams, Wiernik et al., 1990]. Modification of the toxicity of interleukin 2 has been attempted in a BCCA study of administration of interleukin directly into the splenic artery. Preliminary analysis of results indicates that the toxicity is reduced but response rates have been disappointing [Silver and Klasa, 1990 : personal communication].

Monoclonal antibodies directed against malignant cells are under investigation for tumor localisation and treatment. The first patient with malignant lymphoma treated with anti-idiotypic antibodies enjoyed a complete remission lasting 42 months [Meeker, Lowder, Maloney et al., 1985]. Unfortunately, this gratifying result was the exception rather than the rule. Furthermore, potential therapeutic antibodies had to be "custom-made" for the patient since tumor antigenicity, based on surface immunoglobulin expression, is so variable. Monoclonal antibody technology has utilised attached toxins, chemotherapeutic drugs and radio-active isotopes in attempts to kill the targeted cells [Baldwin and Byers, 1985]. In melanoma, therapeutic monoclonal antibodies have been directed against

different melanoma antigens including p97, a proteoglycan, 250kD chondroitin sulfate proteoglycan, GD2 and GD3 gangliosides but clinical results have been disappointing [Rumke, 1986 ; Mastrangelo, Schultz, Kane et al., 1988 ; Dimaggio, Scheinberg, Houghton, 1990]. A phase 1 study of an IgG antibody specific for distinct determinants of the high molecular weight antigen associated with malignant transformation of human melanocytes has been reported [Cascinelli, Attili, Belli et al., 1988]. A phase 2 study of IgG 2a monoclonal [directed against a melanoma-associated antigen] attached to ricin A chain, one of the most poisonous molecules available, failed to produce any tumor regressions [von Wussow, Spitler, Block et al., 1988]. For diagnostic purposes, a monoclonal antibody NKI/beteb detects an antigen on the inside of melanosome membranes and appears specific and sensitive in detecting cells of melanocytic derivation [Vennegoor, Hageman, van Houhuijs et al., 1988].

## **12. Systemic Treatments and Survival.**

The impact of treatments for advanced melanoma has not been impressive. This is important as far as the present study is concerned. Survival is the most important end-point. Evidence that treatments for advanced disease prolong survival in cohorts of patients receiving such treatments is lacking. Difficulties of attributing survival benefits to drug

therapy in responding patients are well known [Simon and Wittes, 1985]. It is therefore acceptable to assume that there is no survival advantage from systemic treatments for relapse in this study. Previous reports of world experience of melanoma discussed in Chapter 2 do not make reference to systemic treatments for recurrent disease suggesting by inference that they confer no significant survival benefit.

### **13. Melanoma Practice in the British Columbia Cancer Agency.**

Malignant melanoma is truly a multi-disciplinary problem involving epidemiology, general practice, dermatology, pathology, surgery, immunology, medical and radiation oncology. In medical oncology at the BCCA, patients with malignant melanoma are assessed shortly after diagnosis, and usually after definitive surgery for consideration of appropriate adjuvant studies and subsequent surveillance. Patients with recurrent disease not amenable to surgery are assessed for palliative therapy with chemotherapy, radiation therapy or symptomatic care.

### **14. Origins and Objectives of Present Research.**

It became apparent that patterns of management of melanoma in the 1970's and 80's were variable between provinces in Canada and between countries. Specifically, recommendations for lymph node dissection and adjuvant therapy differed between Saskatchewan and British

Columbia where I had clinical appointments. Clinical observations of recurrence of relatively thin melanomas, cure in some thick melanomas, hepatic metastases in one patient 37 years after enucleation for choroidal melanoma, sequential single site distant metastases in some patients, the formation of the National Cancer Institute of Canada Melanoma Group, the initiation of a Western Canada Melanoma Study of risk factors and natural history of melanoma all further stimulated my interest.

Finally, the 1980's mark the emergence of "Quality Assurance" in patient care. The importance of outcome analysis has long been recognised but heretofore had been relegated in the list of priorities for many clinicians. Hence, a retrospective review of the British Columbia Cancer Agency experience was commenced. A defined period after the acceptance of histogenic grouping and depth assessment of primary melanomas was chosen and initially a minimum follow-up time of 2 years was proposed. This was later lengthened because of time required for data retrieval.

Although there existed both a Provincial Cancer Registry [where all new cases of cancer are recorded] and a large provincial cancer treatment organisation [the British Columbia Cancer Agency], it would have been extremely difficult to capture all patients' records in a defined period, even



retrospectively. This is in contrast to regions where there are dedicated units providing treatment services, prospective data collection and monitoring of all aspects of the disease with consulting epidemiologists and statisticians. The present review of all patient records at the BCCA was initiated accepting certain limitations. It was known that there would be patients with the disease during the specified time who were not registered and on whom no data would be available. The broader limitations of the retrospective nature of the study were also appreciated. Practically, individual chart review was required since the only computerised patient information available was basic demography, primary site, stage and survival status [alive or dead]. Relative to the sample size, the amount of missing data is acceptable and unlikely to influence conclusions.

The 3 principal original aspects of the thesis are :

1. the study reported in Chapter 2 is the largest outcome analysis of any disease yet undertaken in the BCCA, and is one of the most mature series of melanoma patients in the world literature..
2. Chapter 3 contains one of the largest single institution analyses of prognostic factors for clinical stage 1 patients.
3. the analysis of elective lymph node dissection [Chapter 4] is one of the largest single institution reports in the world literature.

## **15. Future Prospects.**

Progress in the understanding and management of malignant melanoma is continuing, more rapidly in some areas than others. Awareness of the disease and its precursor lesions is increasing. The importance of complete pathological description of the primary has been emphasised. The desirability of inter-disciplinary consultation is exemplified by the evolution of tumor groups and conferences. The necessity for radical excision of primary melanoma has been questioned and the results of lesser surgical procedures are now being examined. The role of elective lymph node dissection will become clearer with two major surgical trial results. High risk groups of patients can now be identified and offered participation in appropriate adjuvant trials. Biological treatments may shortly have an established place in adjuvant therapy. Surveillance after definitive primary treatment is particularly important in detecting local-regional recurrence and monitoring nevi, dysplastic or otherwise. The search for new active drugs in the treatment of metastatic melanoma continues. For the present, however, it appears that the largest reduction in melanoma mortality will come from earlier diagnosis. Information campaigns in areas of even moderate incidence have yielded success [O'Doherty and Mackie, 1988] and more education of the public and their physicians is recommended.



## **CHAPTER 2**

**CUTANEOUS MALIGNANT MELANOMA :**

**BRITISH COLUMBIA**

**CANCER AGENCY**

**EXPERIENCE 1972-1981**

1. **INTRODUCTION.**

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- B. British Columbia Cancer Agency and Cancer Registry.
- C. Review of malignant melanoma from 1972- 1981.
- D. Excluded patients.
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- F. Data collection.
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- G. Primary site, age, growth pattern and stage.
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- I. Correlation of pathology with growth pattern.
- J. Depth of invasion, sex, primary site, growth pattern and stage.
- K. Tumor depth, diameter and volume.
- L. Stage.
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#### 4. **DISCUSSION.**

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- C. Nevi and melanoma.
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- E. Symptom duration.
- F. Primary diameter.
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- H. Histopathology.
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  - ii. Lymphatic and vascular invasion.
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- I. Comparison with various world series.
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  - iv. Depth of invasion.
  - v. Depth of invasion and Clark level.
- J. Tumor volume.
- K. Stage.
- L. Recurrence.
- M. Prognosis in males.
- N. Comparison of outcomes between series.
- O. Future prospects.

## 1. INTRODUCTION

The incidence of malignant melanoma is increasing worldwide with an estimated doubling of incidence rates every 10-17 years [Lee and Canter, 1970 : Schreiber, Bozzo, Moon, 1981 : Thorn, Adami, Bergstrom et al, 1989] and has reached epidemic proportions [Lee, 1990]. However, malignant melanoma presently accounts for only a small proportion of all cancers. In British Columbia, melanoma represented 1.41% of all cancers in 1974, but in 1987 this increased to 3.11% for males and 3.7% for females [Gallagher and McBride, 1987]. In British Columbia and in Nordic countries [Thorn, Adami, Bergstrom et al., 1989], the age adjusted standardised rates have increased 3-5 fold in the last 20 years. Melanoma incidence rates have been monitored in Scandinavia and Australia for many years and there appears to be little if any tendency of increasing incidence to level off [Mackie, 1989].

The rise in melanoma incidence has prompted many studies examining risk and prognostic factors. These suggest that the increase in incidence is real and not due to improved data collection [Hiatt and Fireman, 1986], artifacts of diagnosis or notification, or changes in "cosmetic factors" [McCarthy, Black, Milton, 1980 : Kopf, Bart, Rodriguez-Sains, 1977 : Magnus, 1975]. Established risk factors include the presence of freckles [Osterlind, Tucker, Hou-Jensen et al., 1988],

multiple melanocytic nevi [Swerdlow, English, Mackie et al., 1986 : Green, MacLennan, Suskind, 1985], history of severe sunburn resulting in peeling [Mackie and Aitchison, 1982 : Green, Suskind, Bain, 1985], exposure to ultraviolet light [Gallagher, Elwood, Hill, 1986 : Holman, Armstrong, Hennan et al., 1986 : Retsas, 1983], occupation and socio-economic status [Lee, 1982: Graham, Marshall, Haughey et al., 1985, Gallagher, Elwood, Threfall et al., 1987 : Cooke, Skegg, Fraser, 1984].

Many biological factors influence the course and outcome of malignant melanoma [Balch, Soong, Shaw et al., 1978] including stage, growth pattern, anatomical site, age and sex. This study is a retrospective descriptive review of these and other factors in melanoma patients registered with the British Columbia Cancer Agency [BCCA] from 1972-81.

## **2. MATERIALS AND METHODS**

### **2A. Geographic considerations.**

British Columbia is located on the west coast of Canada and extends from the 49th to the 60th parallel north. The climate ranges from temperate coastal to one of wide extremes in the interior of the province. Figure 1 illustrates the area of the province relative to Europe. From 1971-81 the proportion of persons of British origin decreased from 58 to

51%. Those of European ancestry increased from 18 to 27%, and the proportion of Asians increased from 2.6 to 4.5% [Gallagher and McBride, 1987]. The higher proportion of those of British origin is significant in that persons of Caledonian origin appear to have a higher incidence of malignant melanoma [Mackie, 1989].

## **2B. British Columbia Cancer Agency and Cancer Registry.**

The British Columbia Cancer Foundation was incorporated in 1935 and the Institute was opened in 1938 in Vancouver, British Columbia. Since then, expansion has included a second full service cancer treatment facility in Victoria and 16 consultative clinics throughout the province attended by visiting specialists in Radiation and Medical Oncology. As part of its mandate "to establish, maintain and operate a co-ordinated province-wide programme of cancer care, control and research" the recently renamed British Columbia Cancer Agency [BCCA] maintains a provincial Cancer Registry. The responsibility for the development and maintenance of the provincial Cancer Registry was transferred from the Health Surveillance Registry to the BCCA in 1980. The Registry monitors the incidence of cancer in the community and provides a central cancer data bank for research and education. Starting in 1969, pathologists were required to submit duplicate copies of all pathology reports of malignant disease including in situ and borderline malignancy to the Registry. Referral of new



cancer patients to the BCCA for consultation and treatment can be made by any physician but, in contrast to Registry notification, is voluntary. Patients in this study were seen by Agency oncologists in Vancouver, Victoria and clinics throughout the province.

In 1980 and 1981, the proportion of new patient examinations to total new primary cancers by site was 45% [Cancer Control Agency of BC Annual Report 1981]. Historically this percentage ranges from 40 to 50%. The reasons for this lower consultation rate are varied. For example, treatment may be undertaken at a community level, patients may be in a terminal condition, the diagnosis may be made post mortem, patients may refuse consultation due to age or personal beliefs. Interpretation of the findings in this study assumes that the referred population does not differ significantly from the whole population in terms of epidemiologic, clinical, pathological or natural history factors. If bias exists, it is probably against the referred group, since non-surgical treatment of recurrent melanoma is available almost exclusively through the BCCA.

## **2C. Review of Malignant Melanoma from 1972 - 1981.**

This retrospective study included all new cases of cutaneous malignant melanoma [CMM] diagnosed between June 1, 1972 and May 31, 1981 and registered with BCCA. Follow-up extended to April 30, 1990. In

the defined period of the study there were 1944 patients in BC registered with melanoma in the provincial Cancer Registry. Of these, 1245 were referred to and registered with the BCCA [64% of total population]. Increased awareness and incidence of CMM may account for the high percentage of patients with melanoma entering the Agency for consultation.

## **2D. Excluded Patients.**

Reasons for exclusion from this study of patients registered with the BCCA and diagnosed in the study period are shown in Table 1. Ocular category includes eyeball [33], retina [3], choroid [17], not otherwise specified NOS [32], conjunctiva [3] and cornea [1]. Nasal cavity includes ethmoid sinus [1], maxillary sinus [1] and nasal cavity [5]. Genital organ category includes vulva-NOS [6], scrotum-NOS [1], labium majus [3] and vagina-NOS [3]. Lymph nodes were located on the leg [5], arm [1], and head and neck [2]. The other category includes lesions located in gall bladder, lung, brain, cervix uteri and rectum.

Patients who were registered but not included in the original list in 1983 were excluded [designated "Arbitrary" exclusions in Table 1]. The complete list of patients registered was computer-generated in 1990 as opposed to the manually-created list compiled in 1983. "Registration" exclusions were patients whose diagnosis of primary melanoma occurred

outwith the study period (referral usually being precipitated by recurrence). The 1983 list had 908 patients and the first descriptive analysis was undertaken on these patients. This will be designated "First Analysis". When the data base was updated for recurrence and survival in 1990, there were 17 further excluded patients, The 1990 analysis will be designated "Final Analysis". All Tables with statistical analyses refer to the Final Analysis.

## **2E. Multiple Primary Melanoma.**

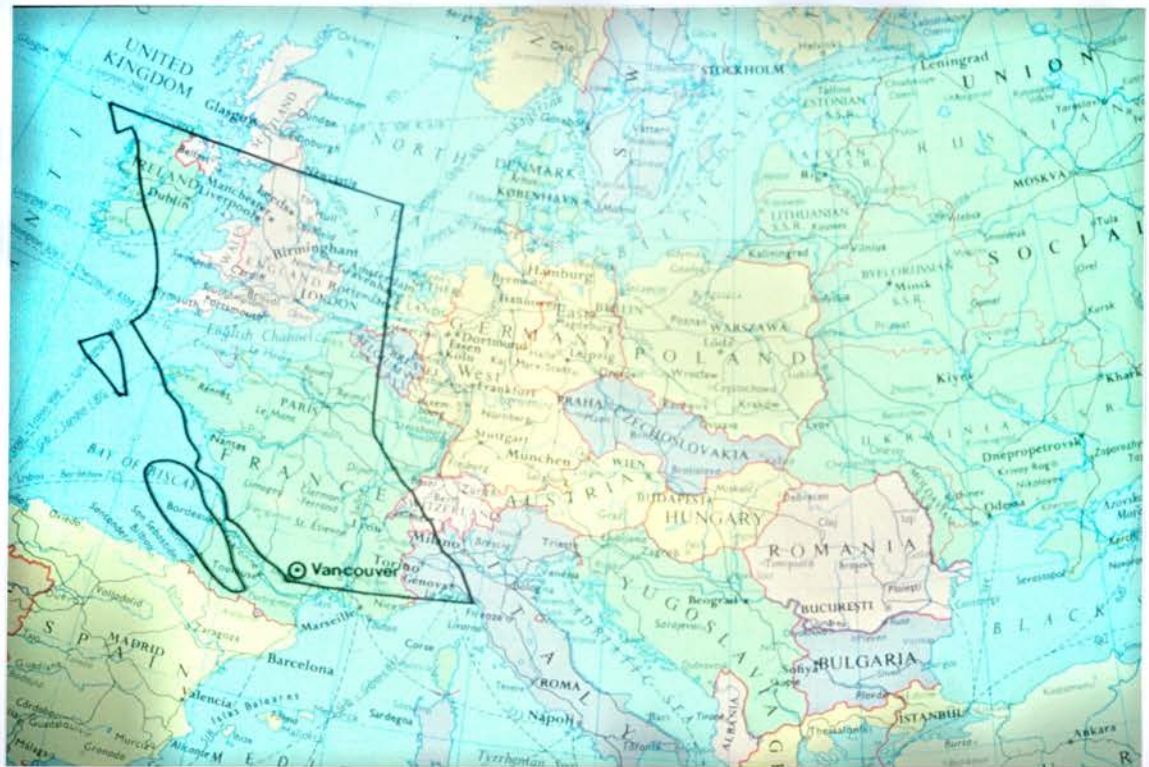
Primary malignant melanoma in multiple sites occurred in 27 [3%] patients at diagnosis, while 25 [2.8%] patients had a subsequent melanoma. These patients were counted only once in the incidence analysis.

## **2F. Data Collection.**

Data on 147 demographic, histopathologic, treatment and outcome variables was extracted from the medical records of the study population. Data was transcribed on to an abstract form [Table 2] and later computerised into a data-base [dBase IV] to facilitate follow-up and statistical analysis. An update of the data base was completed in April 1990.

**Figure 1.**

**British Columbia ; area compared with Europe**





**Table 1.**

**Reasons for exclusion from present study**

REASONS	# CASES	% BCCA SERIES	% BC POPULN.
Eye	89	7.1	4.6
Nasal Cavity	7	0.6	0.4
Genital Organs	15	1.2	0.8
Lymph Nodes	8	0.6	0.4
Other	11	0.9	0.6
Unknown Primary	26	2.1	1.3
Registration	90	7.2	4.6
Arbitrary	108	8.7	5.6
TOTAL	354	33.8	18.3

Footnote : definitions of Registration and Arbitrary exclusions are in the preceding text.



## **2G. Histopathology.**

Histopathology was performed at hospitals throughout the province. The majority of the biopsies were reviewed by 2 BCCA pathologists in Vancouver. Primary growth patterns were described using a standard classification [Clark, Ainsworth, Bernardino et al., 1969]. The four principal growth patterns described in this study were lentigo malignant melanoma [LMM], superficial spreading melanoma [SSM], nodular melanoma [NM] and acral-lentiginous melanoma [ALM]. Differentiation was assessed as a composite of histologic grade, nuclear grade and mitotic rate (Doussal, Tubiana-Hulin, Friedman et al, 1989), as opposed to the presence or absence of various differentiation antigens (Si and Hersey, 1993).

Tumor depth was assessed by Clark's histopathological method [Clark, 1967] and Breslow's micrometer measurement [Breslow, 1970]. The study antedated the universal usage of these methods. Depth measurements were not available on 223 [25%] of the final analysis patients. Depth categorisation was determined from the "T" category of the TNM classification system [American Cancer Society, 1983] : T1 = 0.01-0.75mm, T2 = 0.76-1.50mm, T3 = 1.51-3.0mm and T4 = 3.01+mm. Tumor volume was calculated from diameter and depth [ $Vol = \pi \times \{Diam/2\}^2 \times depth$  ].

**Table 2.**

**Chart Abstract Form**

Study Number XXXXXXXX

Date of Birth XX XX XX

Sex X

Code 1 = M, 2 = F, 9 = unspec.

Previous melanoma history

Yr of Diagnosis Site

XX XX XX XXXXX

XX XX XX XXXXX

# Biopsied benign nevi X

Yr biopsied XX

Basal cell carcinoma [ Year of diagnosis ] XX

Squamous cell carcinoma " " " XX

Other cancer X

Yr of diagnosis	site	morphology
XX	XXXX XXXXX	

[ ICDO site and morphology codes ]

**Current Melanoma ;**

Presenting Symptom	X
--------------------	---

[ code in Table 9 ]

Date of first symptom	XX XX XX
-----------------------	----------

Date of diagnosis	XX XX XX
-------------------	----------

Primary site	XXXXX
--------------	-------

Site at diagnosis	XXXXX
-------------------	-------

if different from primary

Location ; body site ;	R / L	X
------------------------	-------	---

Ant / post	X
------------	---

Med / Lat	X
-----------	---

Clinical appearance at time of diagnosis ;

Max. diameter in mms XX

Surface XX

Code 0, 1 = flat ; 2 = raised ; 3 = both ; 9 = unspec.

Color ; Dominant X

Code 0 = none, 1 = black, 2 = blue, 3 = red, 4 = brown, 5 = grey, 6 = white, 8 = other, 9 = unspec.

Clinical evidence of regression XX

Pathology [as recorded at primary treatment centre] ;

Type of biopsy X

Code 1 = shave, 2 = punch, 3 = excision, 8 = none, 9 = unspec.

Diagnosis X

Code 1 = benign, 2 = in situ, 3 = invasive, 4 = benign, reviewed malignant

Specific diagnosis XX

Code 1 = benign nevus, 2 = atypical lentigo, 3 = atypical junctional nevus, 4 = familial or congenital nevus, 5 = blue nevus, 6 = juvenile melanoma, 7 = borderline melanoma, 8 = lentigo maligna, 9 = lentigo malignant melanoma, 10 = superficial spreading melanoma, 11 = nodular melanoma, 12 = acral melanoma, 13 = mucosal melanoma, 14 = metastatic melanoma, 88 = other [specified], 99 = melanoma type unspecified, 99 = unspecified pathology.

Mitosis	X
Code 1 = low [1/5HPF], 2 = moderate [1/5HPF-1/HPF], 3 = high [1/HPF], 9 = unspec.	
Pigmentation	X
Code 0 = none, 1 = minimal, 2 = moderate, 3 = marked, 4 = pigmented, degree unspec., 5 = unspec.	
Additional configuration	XXX
Code 0= no, 1 = yes for polypoid configuration, regression, ulceration	
Invasion ;	
Clark level	X
Depth measurement [mms]	XXX
Depth group	X
Code 1 = T1, 2 = T2, 3 = T3, 4 = T4,	
Invasion of epidermis	X
Code 0 = no, 1 = yes	
To stratum corneum	X
Lymphatic invasion	X
Venous invasion	X
Dominant cell type	X
Code 1 = epithelioid, 2 = spindle, 3 = mixed, 8 = other, 9 = unspec.	
Differentiation	X
Code 1 = poor, 2 = moderate, 3 = well, 9 = unspec.	



Associated changes	X
Code 0 = none, 1 = dermal or compound nevus, 2 = blue nevus, 3 = junctional nevus, 8 = other, 9 = unspec.	
Inflammatory reaction	X
Code 0 = none, 1 = slight, 2 = moderate, 3 = marked, 9 = unspec.	
Infiltrate type	X
Code 1= lymphocytic, 2 = histiocytic, 3 = plasma cell, 8 = other, 9 = unspec.	
Perilymphatic inflammation	X
Code 0 = none, 1 = present	
Removal	X
Code 0 = not removed, 1 = completely removed, 2 = incompletely removed, 9 = unspec.	
Multiple primary tumors	X
Site	XXXXX
Site	XXXXX
Spread at time of definitive treatment	
Clinical evaluation of first station nodes	X
Code 0 = not involved, 1 = involved, 2 = equivocal, 9 = unspec.	
Pathological evaluation of first station nodes	X
Code 0, 1 = not involved, 2 = involved, 3 = equivocal, 4 = examined, status unknown, 9 = not examined	

If pathology positive, # nodes examined	XX
# positive	XX
Involvement of nodes other	X
than first station nodes	
Stage [MD Anderson]	XX
Performance status [ECOG scale]	X
Surgery ;	X
Code 1 = shave biopsy, 2 = punch or incisional biopsy, 3 = excision biopsy,	
4 = excision + 1-5 cm skin, 5 = excision + 5+ cm skin	
Dissection of first station nodes	X
Code 0, 2 = no, 1 = yes, 9 = unspec.	
Date of definitive surgery	XX XX XX
Date of dissection of first station nodes	XX XX XX
Immunotherapy	XX
Code 0 = none, 1 = BCG [NCIC Trial], 2 = BCG [BCCA], 3 = BCG	
intralesional, 4 = levamisole, 5 = C Parvum, 6 = BCG + levamisole, 7 =	
BCG + C parvum, 8 = other immunotherapy, 98 =unspecified	
immunotherapy given, 99 = unspec.	
Date of commencement of immunotherapy	XX XX XX
Duration of immunotherapy [mo.]	XX
Adjuvant chemotherapy	XX
Code 1 = DTIC , 2 = DTIC 1 Gm x 3, 1 Gm q 4 wks, 3 = DTIC 850 mg/m <sup>2</sup> ,	

4 = DTIC 250 mg/m<sup>2</sup>, q 4 wks, 5 = Cisplatin, 6 = VCR/PCZ/CCNU, 7 = HD-MTX, 8 = other, 9 = unspec.

Date of commencement of chemotherapy XX XX XX

# courses of DTIC XX

Radiotherapy XX

Code 0 = none, 1 = to primary, 2 = to first station nodes, 3 = to tumor and first station nodes, 4 = to metastatic sites, 5 = to 1/2 body, 8 = other, 98 = unspec. radiotherapy given, 99 = unspec.

Date of commencement of radiotherapy XX XX XX

## RECURRENCE

Date of first recurrence XX XX

Sites of first recurrence XXXXXXXX

Code 0,1 = none, 01 = local, 02 = within 5 cm of primary, 03 = in transit, 04 = first station nodes, 05 = liver, 06 = lung, 07 = brain, 08 = GI tract, 09 = skin, 10 = subcutaneous, 11 = bone, 12 = marrow, 13 = other nodes, 88 = other, 98 = metastases, site unspec., 99 = residual disease

Type ; single / multiple / unknown X

Subsequent primary melanoma XX XX

Date of diagnosis XXXXXX

Site XXXXX

Other subsequent primary tumor

Date of diagnosis XX XX

Site	XXXX
Morphology	XXXXX
Treatment of recurrence	
1. Surgery	X
Code 0, 1 = none, 2 = re-excision of primary, 3 = Regional node dissection, 4 = amputation, 5 = excision of single distant metastasis, 9 = unspec.	
Surgical excision	X
Code 1 = complete, 2 = gross residual, 3 = micro. residual, 9 = unspec.	
Date of relapse after radical surgery	XX XX XX
for first recurrence	
2. Radiotherapy	X
3. Chemotherapy	X
# of chemotherapy cycles	XX
Response to initial chemotherapy	X
Code 1 = Complete response, 2 = partial, 3 = minor, 4 = stable, 5 = progression, 9 = indeterminate	
Duration of response [mo]	XX
Subsequent chemotherapy	X
# of chemotherapy cycles	XX
Response to second chemotherapy	X
Duration of response	XX
Subsequent chemotherapy	X

# of chemotherapy cycles	XX
Response to third chemotherapy agent	X
Duration of response	XX
Tamoxifen treatment	X
Code 0, 2 = no, 1 = yes	
Other hormone treatment	X
Hormone receptor status of melanoma	XX
fmol/mg	
Duration of tamoxifen therapy [mo]	XX
Response to hormone treatment	X
Duration of response	XX
BCG immunotherapy for recurrence	X
Duration [mo]	XX
Response to BCG	X
Duration of response	XX
Survival ;	
Date of death	XX XX XX
Date of last review alive	XX XX XX
Status	XX
00 = lost to follow-up	
01 = alive, disease-free since primary treatment	
02 = alive, disease-free due to regression since primary treatment	



03 = alive, disease present continuously since diagnosis	
04 = alive, disease present from recurrence after disease-free interval	
05 = alive, current disease status unknown	
06 = dead from disease	
07 = dead from other causes, disease present	
08 = dead from other causes, disease absent	
09 = dead from other causes, disease status unknown	
33 = alive, disease free since treatment for recurrence	
Autopsy	X
Date of abstract	XX XX

## **2H. Age, Site, Stage Description.**

Age refers to patient's age at pathologic diagnosis. Categorisation of age was determined by partitioning melanoma mortality distribution. Patients were divided into 3 categories : 0-39, 40-59 and 60-99. The International Classification of Disease [ICD] 8th. version was used to categorise primary sites [Table 3]. Four principal categories were used : head and neck [H & N], trunk [T], lower limb [LL] and upper limb [UL]. Stage was categorised [Table 4] using a modification of the MD Anderson Hospital System [Haskell, 1980] as local [stage 1 and 2], regional [stage 3] and distant [stage 4]. Survival times were calculated from date of diagnosis to death, last written or physician contact. Mortality data was

provided by the Division of Vital Statistics of the Provincial Ministry of Health [Gallagher and McBride, 1987].

## **2I. Statistical Methods.**

Data was analysed with the Statistical Package for Social Science [SPSS-X release 3.1]. Trends in incidence were analysed using simple linear regression analysis. The model utility test was used to test statistical significance. Time intervals between events during the course of disease were compared for men and women by calculating mean and median times in months. Mann-Whitney U-tests were used to test the differences between sexes. Age standardised rates based on the number of tumors were adapted to those of the BC population at the 1971 census by the direct method of standardisation [Waterhouse, 1980]. All population data were obtained from Census Canada publications [Statistics Canada, 1988]. The age standardised rate calculates cancer risks by age group eliminating the effects of different population sizes and changing proportion of older people in later years [Gallagher and McBride, 1987].

Survival curves were generated using the product limit method [Kaplan and Meier, 1958] with a biomedical computer program BMDP [Dixon, 1981], version 1988. This method allowed the inclusion of patients lost to follow-up. The Tarone-Ware chi-squared analysis was used to

determine the relationships between the different variables. Cases with missing data were excluded from the relevant analysis procedures. A level of significance of 5% or less was considered significant in all statistical tests used in this report. Means and standard deviations are all reported in the standard notation : mean +/- standard deviation. The mean survival times were calculated using survival times of cases with a response [a death from melanoma]. All statements of percentage refer to percentage of total cases in the study population [First or Final Analysis] unless otherwise stated.

Table 3 over/

**Table 3.**  
**Primary Site Codes**

1730 Lip}	
1731 Inner canthus}	
1731 Palpebra}	<b>Head and Neck</b>
1732 Ear}	
1733 Face}	
1734 Neck}	
1735 Trunk }	<b>Trunk</b>
1736 Upper limb }	<b>Upper limb</b>
1737 Lower limb }	<b>Lower limb</b>
1841} Female external genitalia	
1844}	
1903 Conjunctiva	
1963 Lymph nodes of axilla or arm	
9999 Unspecified	
Suffix;1 :Right;2 : Left; 0,9 :Unknown	

**Table 4. STAGING SYSTEM**

Stage 0	Lentigo Maligna
Stage 1A	Intact Primary
1B	Primary locally excised
1C	Multiple primaries
Stage 2	Local spread within 5cm from Primary
Stage 3	Regional Metastases >5cm from Primary
3A	In Transit
3B1	Regional nodes clinically and pathologically +ve
3B2	Nodes clinically - but pathologically +ve
3B3	Primary unknown : nodal presentn. of met. melanoma
3B4	Previous primary : nodal recurrence
3AB	Intradermal mets + regional nodes
Stage 4	Distant hematogenous metastases
4A	Single
4B	Multiple
4B1	Skin only
4B2	Visceral
4B3	Lymph nodes

### **3. RESULTS**

#### **3A. Incidence and Mortality Rates.**

Age-standardised incidence rates of CMM in BC have increased significantly for both males and females [Figure 2]. Rates for males and females from 1971-88 increased 5-fold and 3-fold respectively. Linear regression analysis gave a slope of 0.459 [ $r^2=0.942$  ;  $p<0.0001$ ] for males and a slope of 0.463 [ $r^2=0.816$  ;  $p<0.0001$ ] for females. In 1988, age-standardised incidences of melanoma in males and females were 11.5 and 12.8 per 100,000. In 1983, the age-standardised death rate per 100,000 in Canada and BC was 1.8 [Gallagher and McBride, 1987]. Mortality rates are also shown in Figure 2.

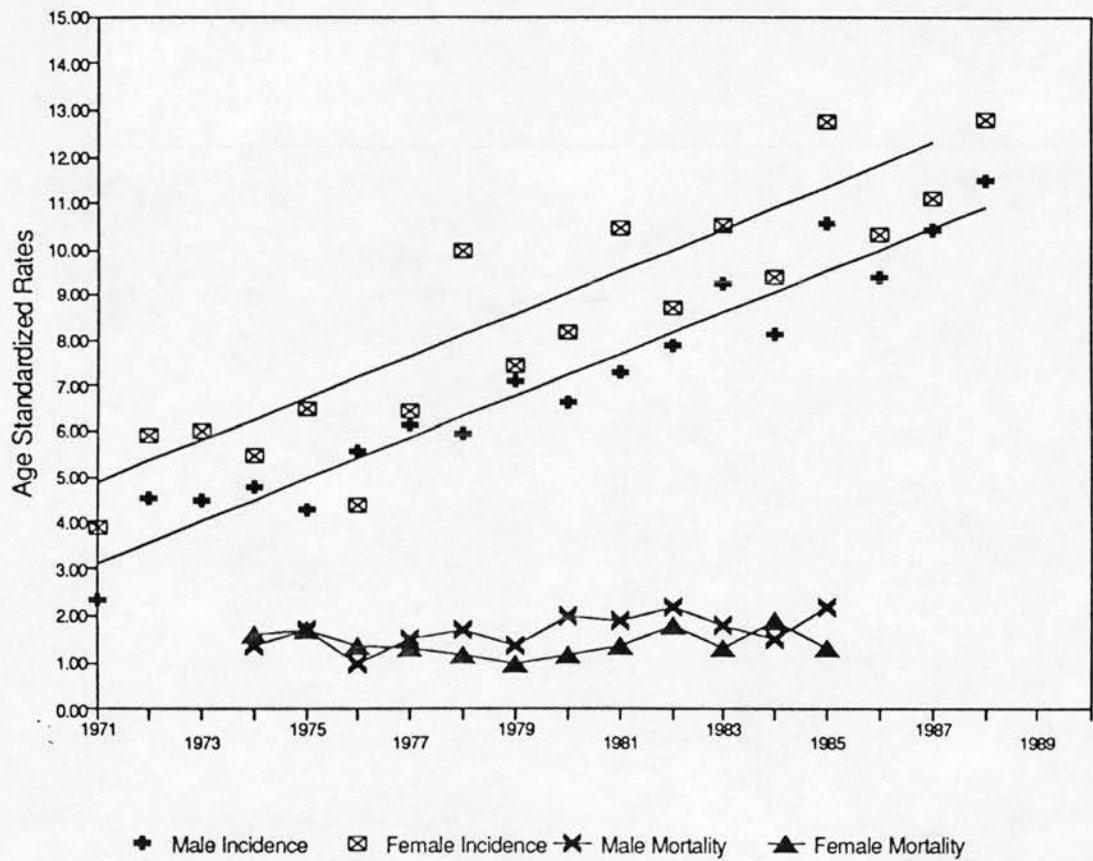
#### **3B. Age and Sex Distribution.**

Sex incidence according to age group and year of diagnosis is summarised in Figures 3 and 4. In Figure 3, Age Group on the X axis refers to the prior decade eg 30 = third decade. The sex incidence in each age group was virtually equal with the exception of a striking dominance of female melanoma in the 4th decade. The incidence for 1981 in Figure 4 is projected from the 6 month period of the study. The increasing incidence from the Cancer Registry data in Figure 1 is paralleled in the increasing incidence measured by BCCA referrals [Figure 4].



Figure 2.

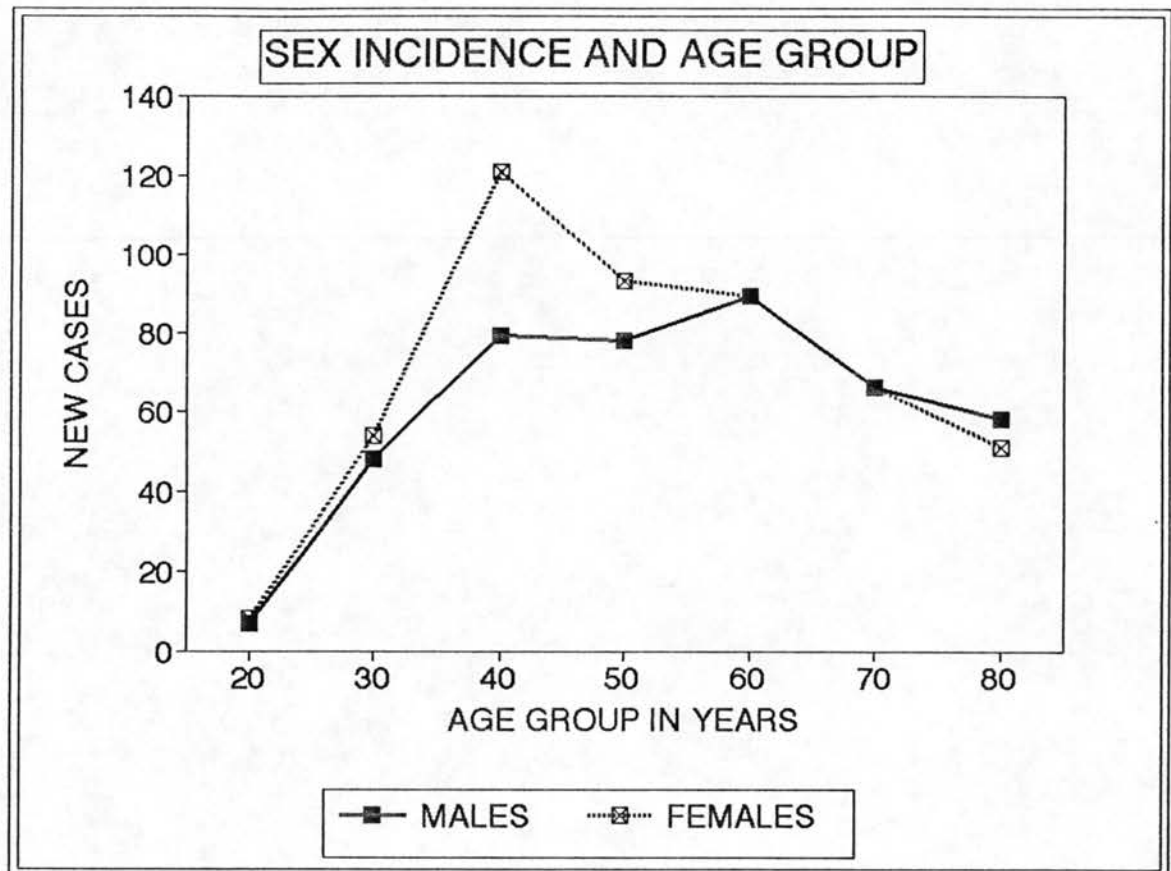
British Columbia Melanoma incidence and mortality  
1971-1988.



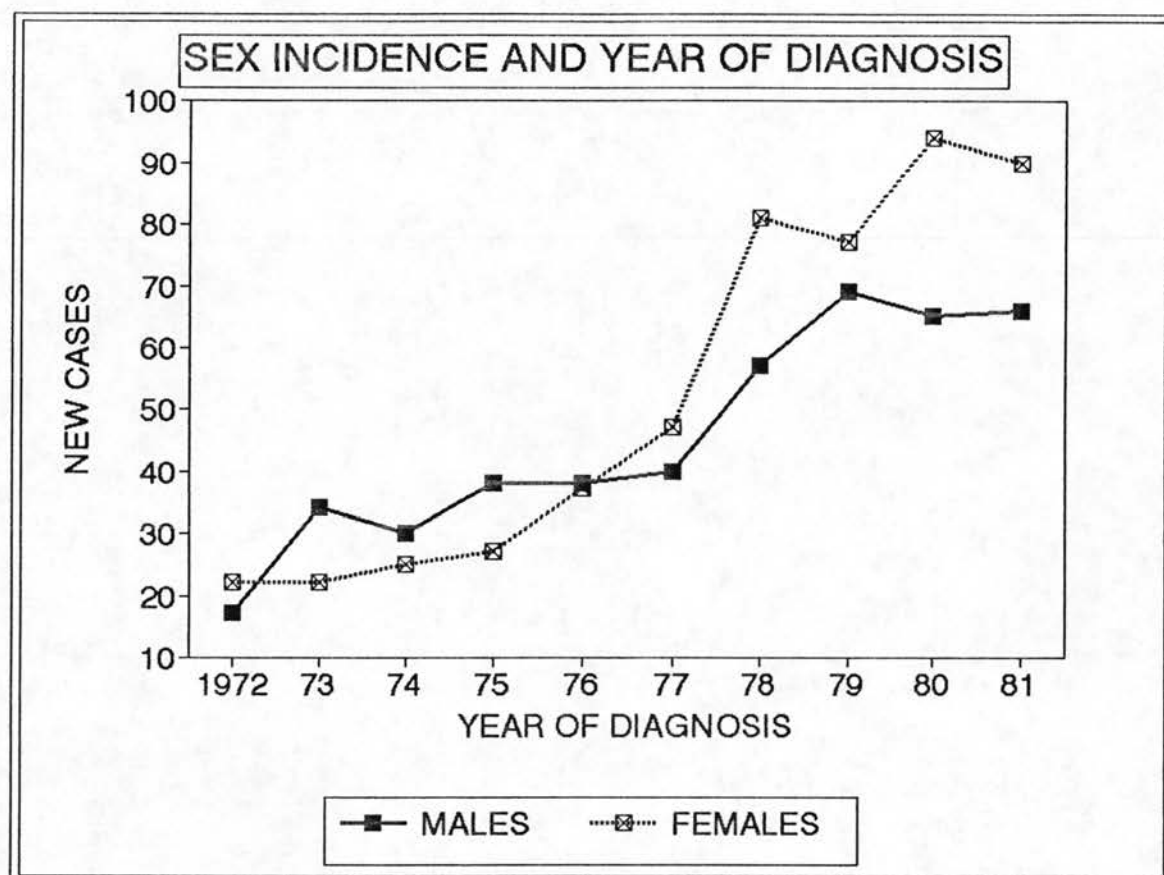
Data was analysed to determine if there was any change in melanoma incidence by age at diagnosis over the period of study. Analysis of incidence by age group is presented in Figure 5. In 1978-80, there was an increase in melanoma incidence in the 4th decade, rising from 10-22% of melanomas each year from 1972-77 to between 25-27% of melanomas. This occurred at a time when BCCA incidence increased quite markedly [from 1977-78]. This is confirmed for females in the Cancer Registry data but not for males. Changing referral patterns could also influence BCCA incidence data.

In the Final Analysis, there were 419 males and 472 females with an overall female : male ratio of 1.13 : 1. This was not a constant ratio throughout the period of the study. From 1972-75 the ratio averaged 0.84 : 1 and from 1976-81, 1.25 : 1. Overall median age was 47 years, mean 48.2 +/-16.9. Median age for males was 49 years and 44.0 years for females. For males, mean age was 49.7 +/- 17.4 and for females 46.9 +/- 16.3 years. The differences between the means was not statistically significant. Median ages for primary tumors in major body sites are presented in Table 5. Overall there was little difference between median ages for all primary sites except head and neck where median ages were higher. Females had lower median ages for primaries on the trunk and upper limb. The range of median ages was narrower for males than for females : 46-58 years for males and 39.5-56 years for females.

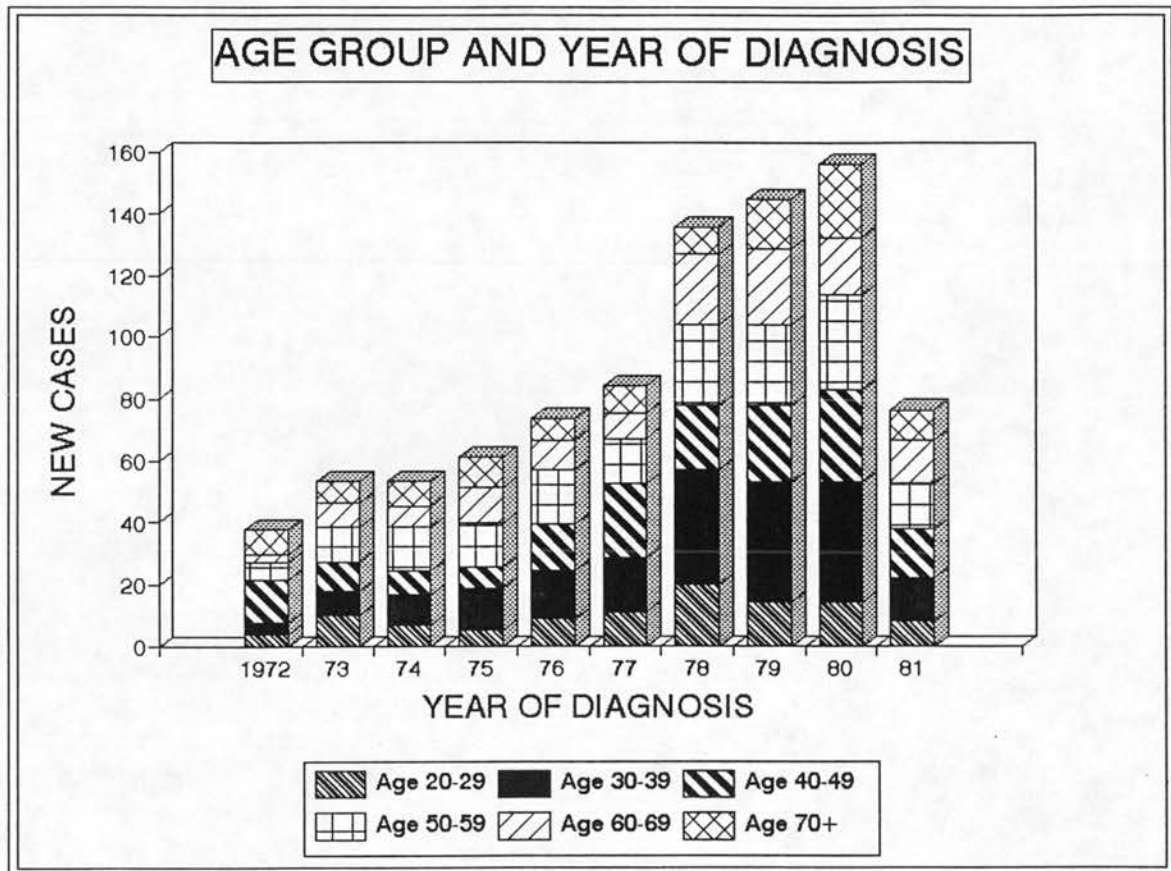
Figure 3



**Figure 4**



**Figure 5**



**Table 5.**

**Median and mean [brackets] ages in years at diagnosis among the 4 major primary sites.**

SEX	HEAD & NECK	TRUNK	UPPER LIMB	LOWER LIMB
M	58 [57.4],	46 [46.4],	48 [49.8],	48 [48.1]
F	56 [54.5],	39.5 [42.5],	43 [47.1],	47 [46.7]

### **3C. Clinical History.**

Of 908 patients, 11 had a history of 1 previous melanoma and 2 had 2 previous melanomas. Basal cell carcinoma occurred in 50 [5.5%] and squamous cell skin carcinoma in 11 [1.2%] of patients. Benign nevi were previously removed in 179 [19.7%] patients, 97 with 1, 43 with 2, 21 with 3 and 18 with 4 or more.

Change in size of a mole was the commonest [43%] presenting symptom. Other symptoms were development of a new mole [13%],

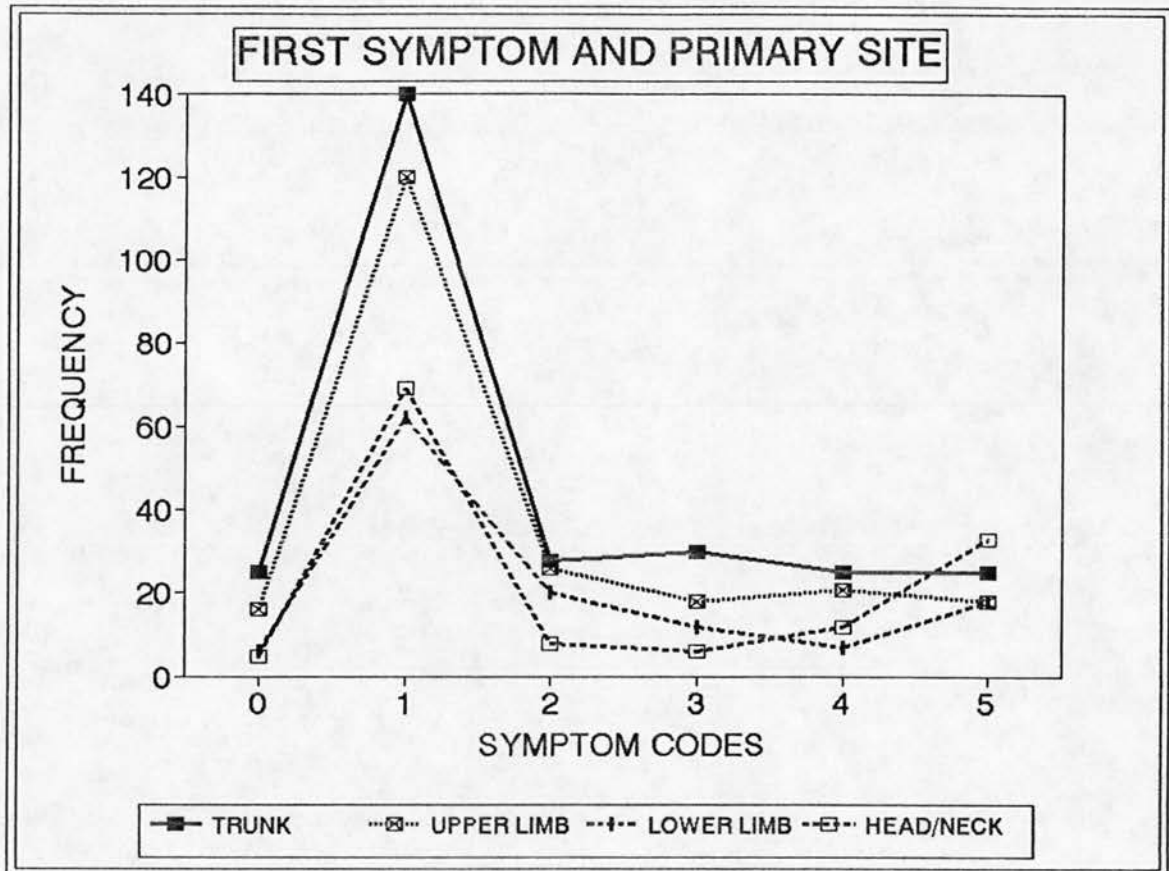


change in color [9%], bleeding or ulceration [8%] and pain/tenderness/itch [8%] in a mole. Melanoma was recognised incidentally by a physician in 7% of cases in patients who did not bring it to their physician's attention. Clinical description of primary tumor diameter is summarised ; 0-5mm, 15% : 6-10mm, 34% : 11-15mm, 21% : 16-20mm, 10% : 21-30mm, 7% : 31-40mm, 1% : 41+mm, 1% : unspecified, 12%.

Presenting symptoms according to primary site are summarised in Figure 6. Change in size of a mole was the commonest symptom in all sites [43-46%]. Incidental recognition by physicians varied from 5% for H & N to 8% for trunk primaries. Bleeding or ulceration was the presenting symptom in 4% of upper limb primaries, 8% of trunk and 9% for H & N and lower limb. Development of a new mole varied from 8% for trunk, 14% for upper limb, 16% for lower limb to 21% for head and neck primaries.

Figure 6, 7 over/

Figure 6



**SYMPTOM CODES**

- 0 recognised by physician
- 1 change in size of mole
- 2 color change
- 3 pain/itch
- 4 bleeding/ulceration
- 5 new mole
- 6 irregular contour
- 7 nodal enlargement
- 8 nodal pain
- 9 other

Figure 6 cont

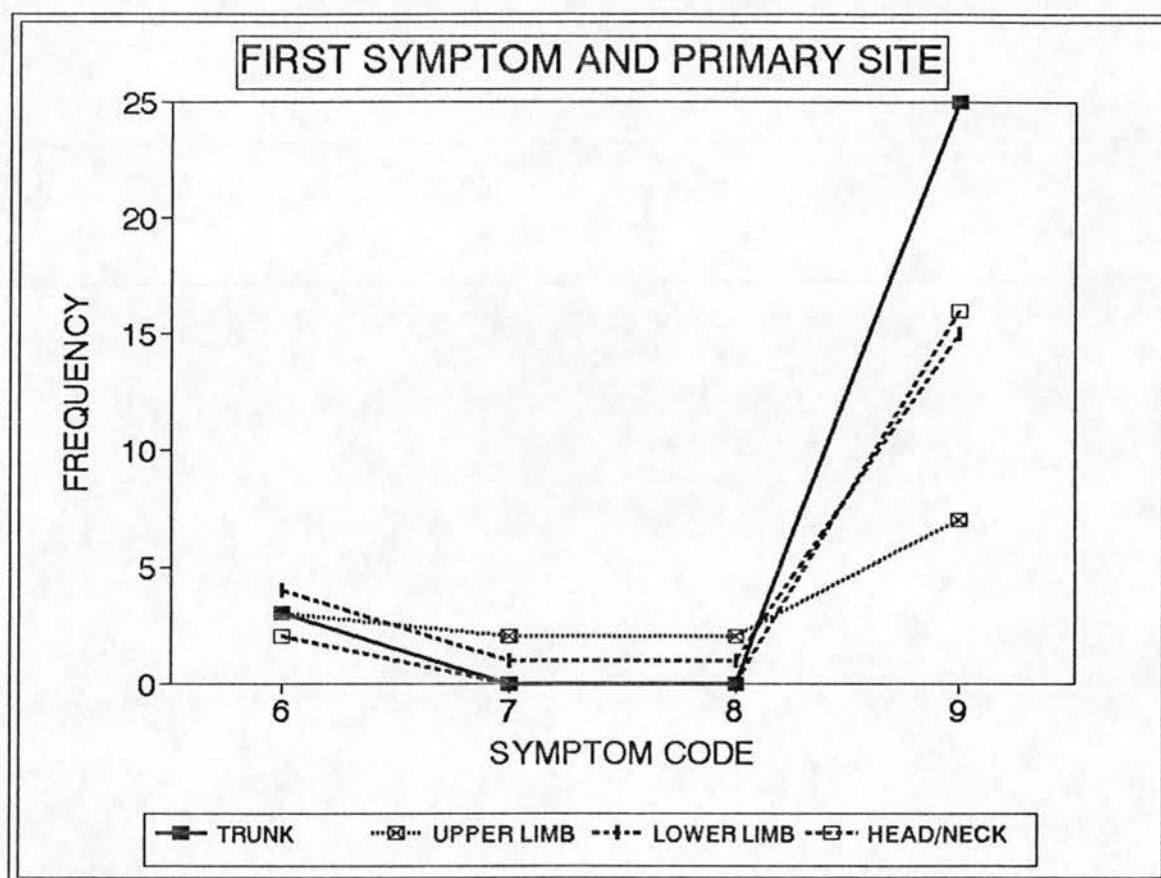
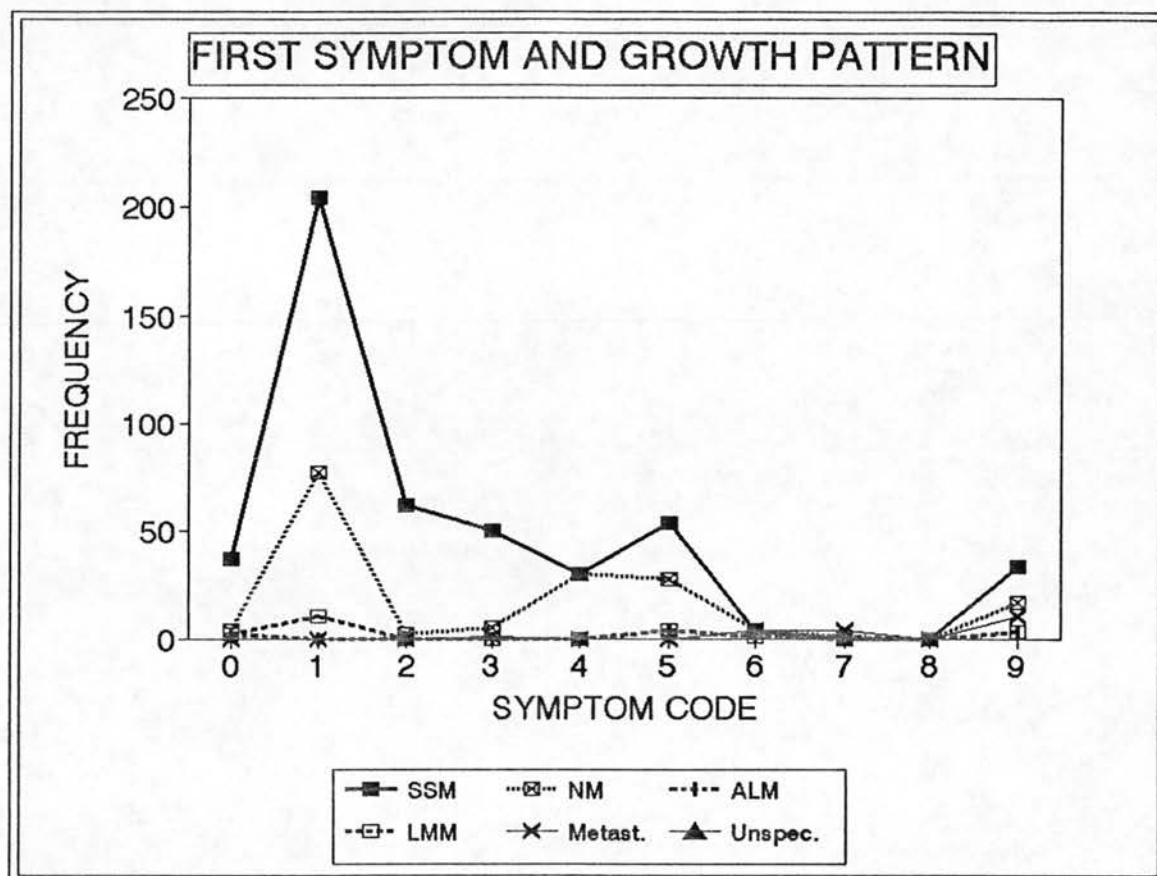


Figure 7



First symptoms according to growth pattern are summarised in Figure 7. Change in size of a mole was the presenting symptom with virtually equal frequency in LMM [45%], SSM [43%] and NM [44%]. Pain/tenderness/itch occurred more frequently in NM than SSM [15% vs 6%]. Development of a new mole was reported by 11% of SSM patients and 16% of NM patients.

Duration of presenting symptoms before diagnosis according to primary growth pattern is summarised in Figure 8. Shortest symptom times were associated with metastatic melanoma and ALM. Symptom times of up to 1 year occurred in 74% of NM and 66% of SSM. Symptom times of 2+ years occurred in 41% of LMM, 21% of SSM and 14% of NM.

Time intervals in months for important events in the natural history of melanoma are summarised in Table 6. Total refers to the number of cases included in each analysis. The only interval of statistical significance was survival time from diagnosis. Females had a longer time between diagnosis and first recurrence with a corresponding increase in time to death. The natural history of recurrent disease measured by time from recurrence to death was similar between the sexes.

Disease-free intervals are defined as periods of time between

diagnosis and events in the course of disease. There are 4 possible groups of cases with respect to disease-free intervals : those who had no recurrence or death, those who had recurrence but no death, those who had no clinical recurrence but died from disease and those who had both recurrence and death from melanoma. The only significant disease-free intervals for males and females was in patients experiencing both recurrence and death from melanoma [ $p = 0.047$ ].

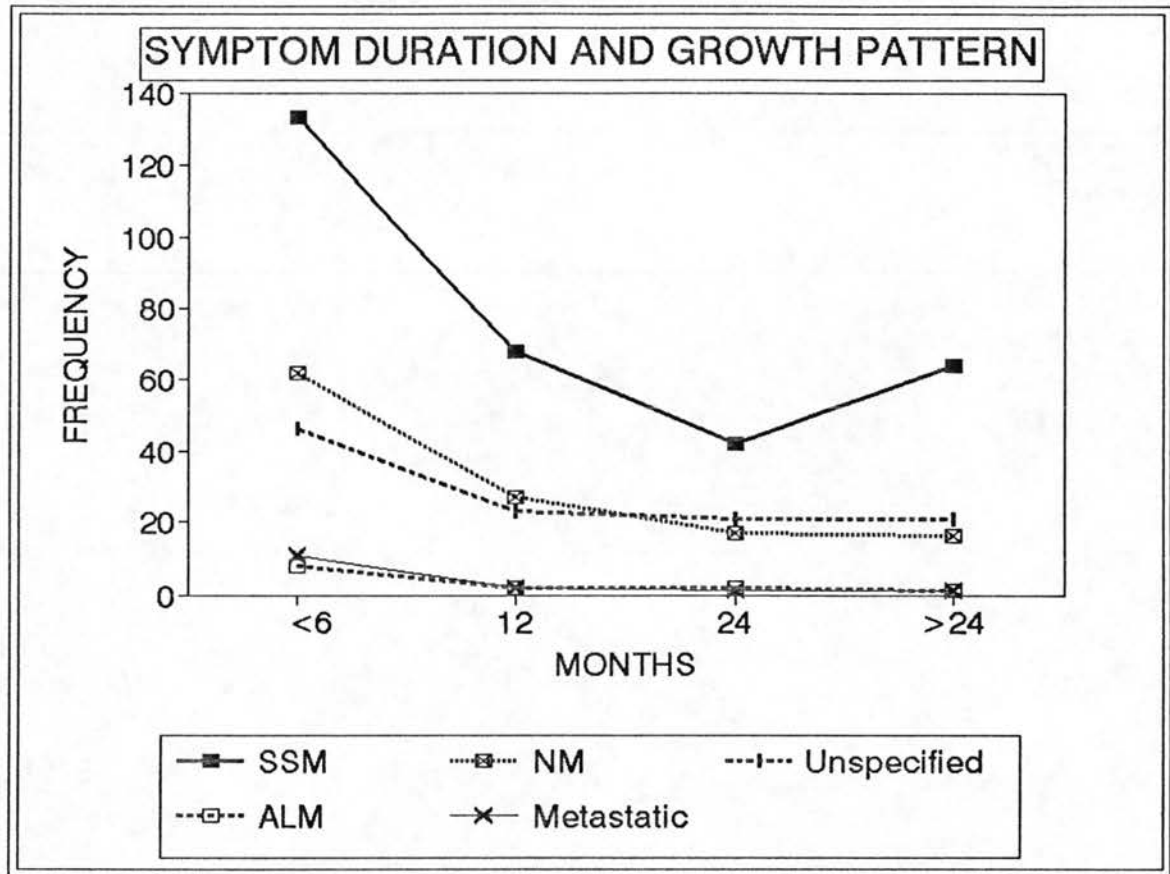
### **3D. Clinical Description of Primary Tumor.**

Dominant primary colors were brown [42%], black [15%], grey [11%], red [4%], blue [3.5%], other/unspecified in 24%. Ulceration was described in 21.7%. The primary was flat in 21%, raised in 51%, both raised and flat in 8%, and 20% were unspecified/missing. Primary tumor diameters according to year of diagnosis are presented in Figure 9. There did not appear to be any trend towards decrease in primary tumor diameter over the decade.

Figure 8 over/



Figure 8



**Table 6.**

**Time intervals for events in the course of disease.**

**Time in months, except survival median, mean and SD  
[years].**

<b>TIME</b>	<b>#</b>	<b>#</b>	<b>Medn</b>		<b>Mean</b>		<b>StDev</b>		<b>p val.</b>
	<b>M</b>	<b>F</b>	<b>M</b>	<b>F</b>	<b>M</b>	<b>F</b>	<b>M</b>	<b>F</b>	
To Diagn.	300	342	5.6	6.2	13.6	17.8	31.2	35. 0	0.13
To 1st Recurr.	185	151	19.7	24.2	29.7	36.3	27.8	32. 9	0.07
1st-2nd Recurr.	67	56	7.1	6.0	12.2	13.5	15.6	21. 1	0.63
Recurr. to death	159	117	10.9	11.6	17.6	19.6	21.1	23. 9	0.6
Survival	417	466	749	892	7.03	8.42	4.26	3.9	<0.00 01

Footnotes : Only first recurrences treated surgically had 2nd recurrence date recorded. "Recurr to death" = Time from **first** recurrence to death.

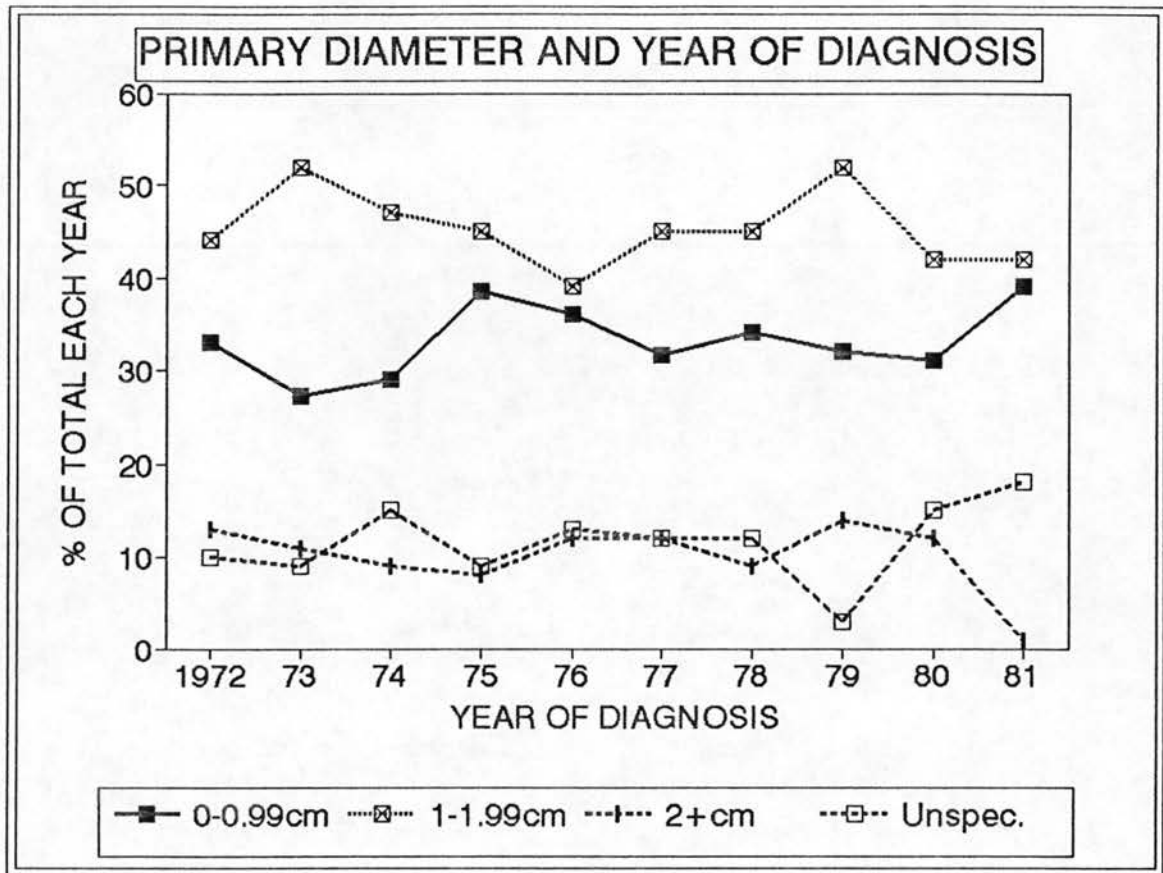
### **3E. Biopsy and Excision.**

Excision biopsies were performed in 774 [85%] patients, punch biopsy in 123 [13.5%], shave biopsy in 1, no biopsy in 7, and 3 were unspecified. After biopsy, excision of the primary lesion with 5+cm [total width] of skin was performed in 576 [63.4%] of patients. Excision with 1-5 cm skin was performed in 234 [25.8%], excision alone in 70 [7.7%]. Punch or incisional biopsy alone was performed in 15, shave biopsy alone in 1, and 12 excisions were unspecified in size.

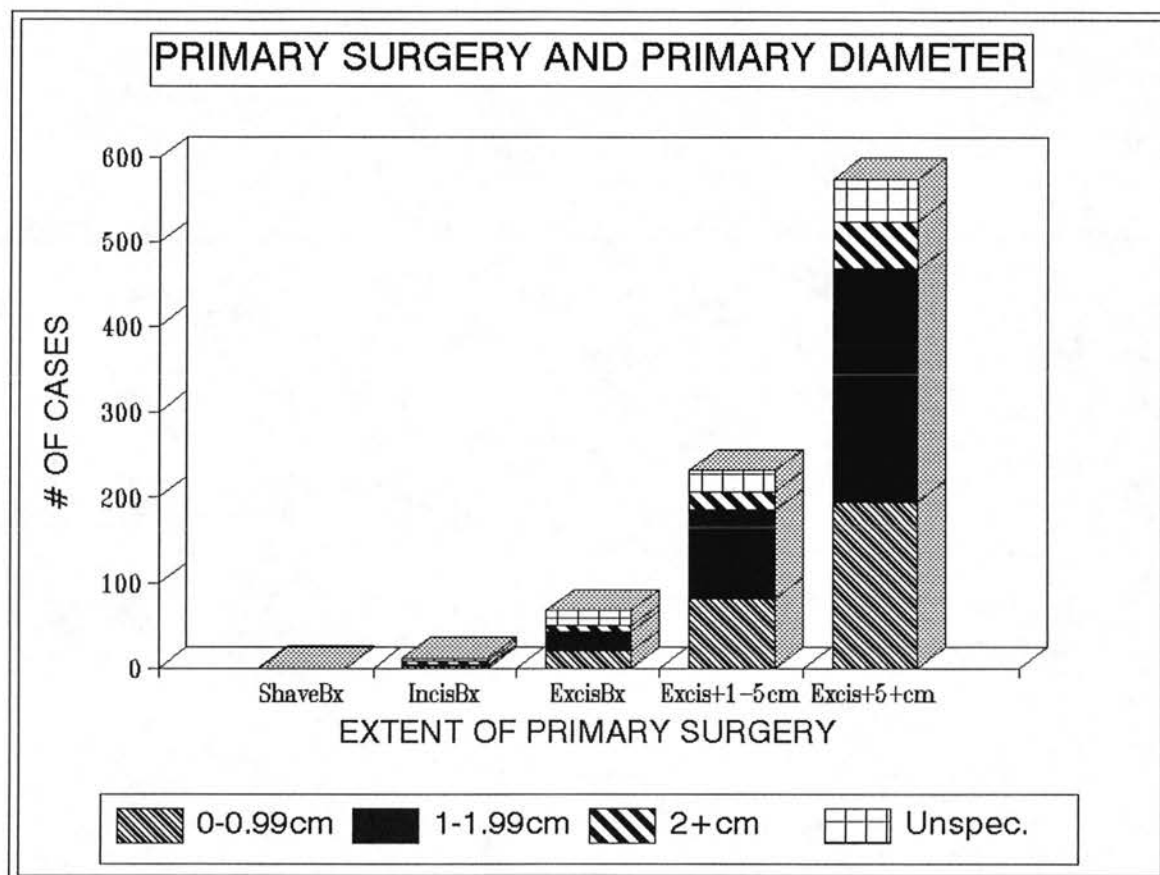
The extent of primary surgery in relation to diameter of primary is summarised in Figure 10. Excision of the primary with at least 1 cm normal skin was undertaken in 85-94% of patients in whom the excision specimen was measured. Over the period 1972-81 the proportions of patients having excisions with 5+ cm skin were 56, 55, 60, 55, 60, 70, 62, 76, 61 and 65%.

Extent of primary surgery in relation to primary tumor thickness is shown in Figure 11. All but 3 patients with specified tumor depth had at least an excision of the primary. Excision of 1 +cm skin was undertaken in 94, 96, 96 and 89% of T 1, 2, 3 and 4 primaries respectively. Excision of 5 + cm skin was undertaken in 57, 76, 74 and 68% of T 1, 2, 3 and 4 primaries respectively.

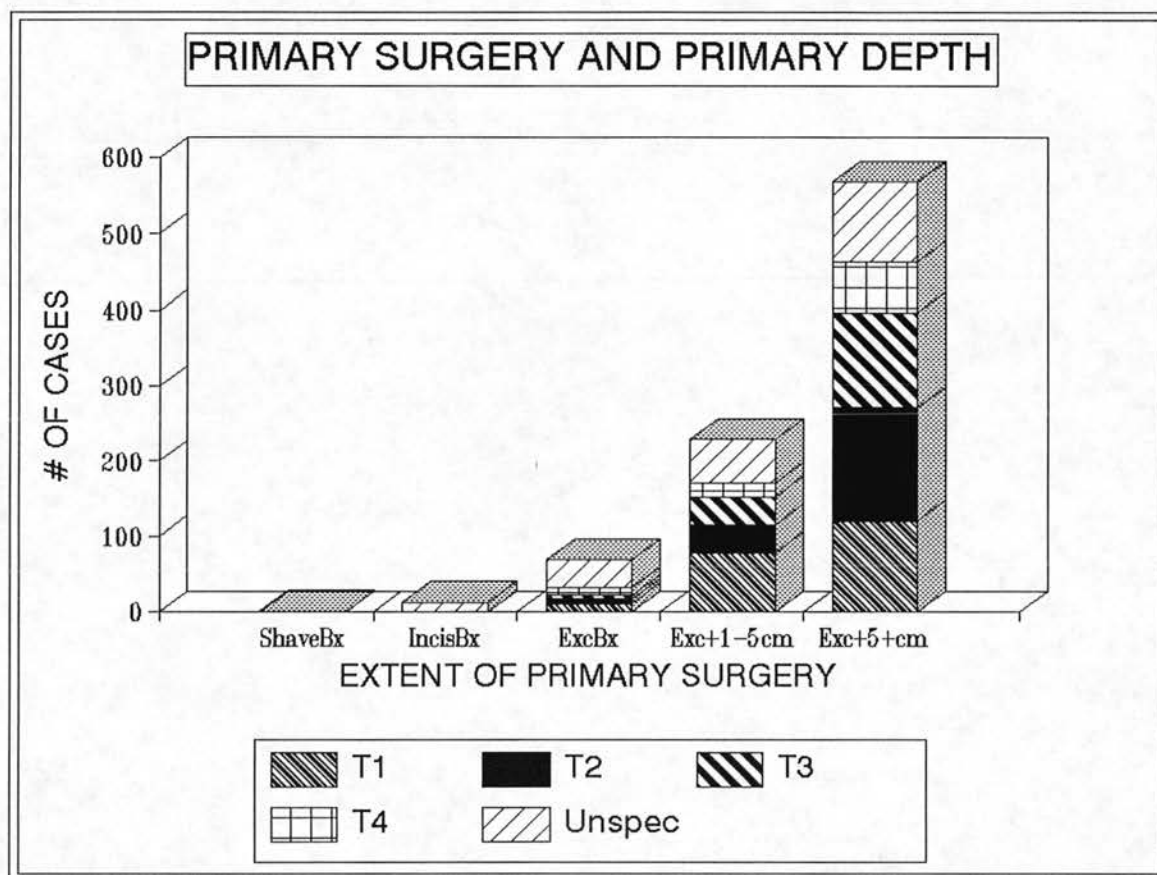
Figure 9



**Figure 10**



**Figure 11**





### **3F. Pathological Description.**

#### **a. General.**

Histology was invasive in 863 [95%], in situ in 22 [2.4%], benign and subsequently reviewed as malignant in 15 [1.7%], benign in 3 and unspecified in 4 cases. Pigmentation was described in 98.9% of cases, to minimal degree in 16%, moderate in 21%, marked in 16% and unspecified degree in 41%. The following features and frequencies were present ; regression, 7.4% : polypoid configuration, 8.8% : ulceration, 24.9% : lymphatic invasion, 6.3% : venous invasion, 0.8%. Cell type was epithelioid in 25.4%, spindle in 10.4%, mixed in 7.8% and unspecified in 56.2%. Differentiation was poor in 3.9%, moderate in 7%, good in 4.2% and unspecified in 84.8%. Mitotic rate was low in 24%, moderate in 23%, high in 11.6% and unspecified in 42%. Associated dermal nevus, blue nevus and junctional nevus were present in 8.7%, 0.6% and 4.6% of cases respectively. Inflammatory reactions were absent in 5.8%, and present to slight degree in 24%, moderate 27% and marked in 14.5% of cases ; 28% were unspecified. Peri-lymphatic inflammation was present in 6.5%, absent in 89.1% and unspecified in 4.3% of cases. Invasion to the stratum corneum was reported in 48% of cases.

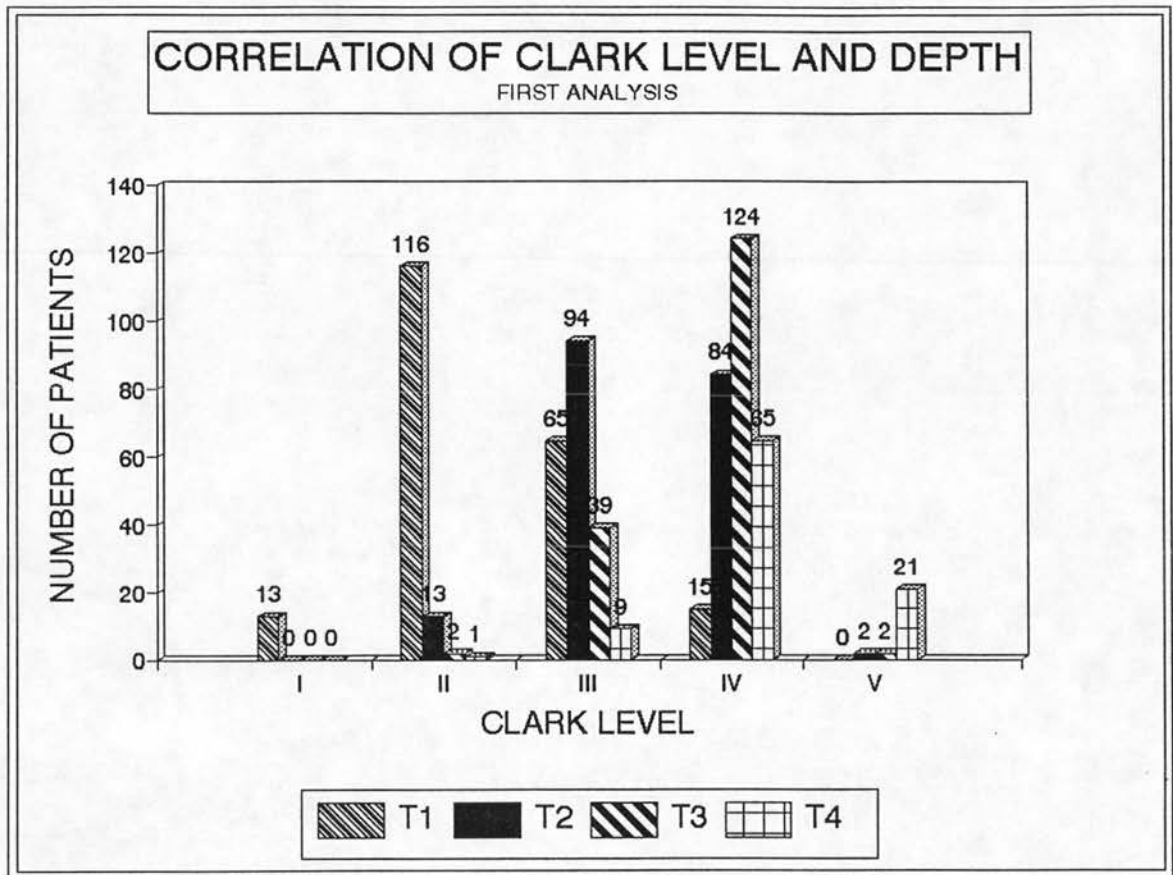
### **b. Depth Assessment.**

Depth assessments by Clark level and Micrometer [T 1 - 4 categories] are presented and correlated in Figure 12. Final Analysis correlates are shown in Figure 13. Within Clark levels III and IV, there was a wide variation in tumor thickness. Similarly, in all groups of tumor thickness [T 1-4], there was considerable variation in Clark levels.

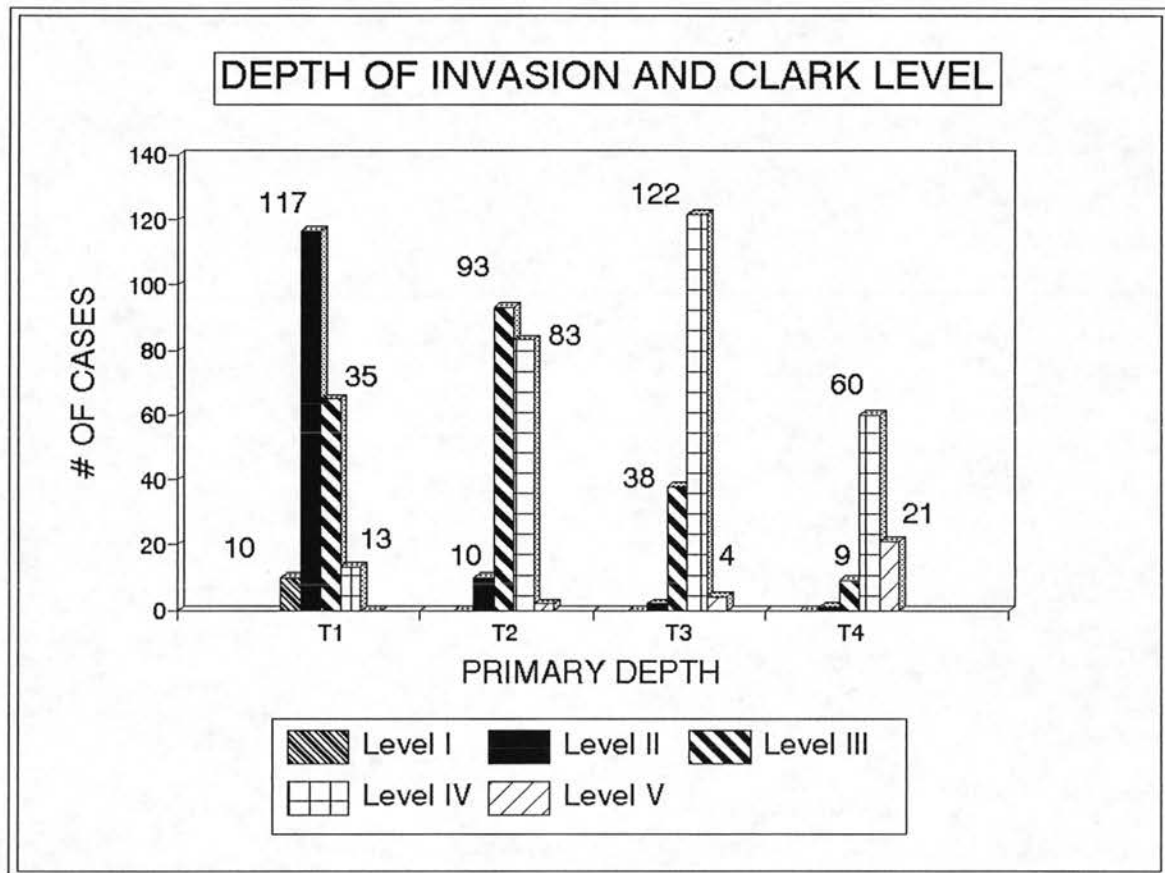
### **3G. Primary Site, Age, Growth Pattern and Stage.**

Table 7 illustrates the Final Analysis of patients according to primary site, sex, age, Clark level, growth patterns and stage. Predominant primary sites were trunk for males [46% of total male population] and lower limb for females [44% of total female population]. Trunk primaries occurred predominantly under 60 years [81% of all male and 86% of all female trunk primaries] and were the commonest primaries in all decades through to age 60. Lower limb and trunk primary sites were virtually equal in frequency in the 7th decade and head and neck was the commonest [45%] site in those patients over 70. 48% of all male and 44% of all female head and neck primaries occurred over 60 years. Primaries distributed on the lower limbs were similar to trunk primaries : 74% of all male and 80% of all female lower limb primaries occurred under 60 years.

**Figure 12**



**Figure 13**



Distribution of specified growth patterns was SSM [65%], NM [25%], LMM [5%] and ALM [2%]. Growth pattern according to age is illustrated in Figure 14. LMM incidence increased with age and occurred mainly on the head and neck [80%]. Only 13% of all LMM occurred under age 50 years. SSM declined in incidence over age 60 years.

### **3H. Depth of Invasion and Year of Diagnosis.**

Clark level of invasion according to year of diagnosis is presented in Figure 15. The proportion of level 1 and 2 primaries has increased over the decade 1972-81. In the first 5 years, level 1 and 2 accounted for 13% of all cases with specified depth and this increased to 24% in the second 5 years. The proportion of level V primaries decreased from 12% in the first 5 years to 5% in the second. Values for 1981 were projected from the 6 month figures available for that year.

Table 7, Figure 14 and 15 over /

**Table 7.**

**Number of new cases of Cutaneous Malignant Melanoma categorised by primary site and sex, age, Clark levels, growth pattern and stage.**

	Total	H &	N	TR	TR	UL	UL	LL	LL
		M	F	M	F	M	F	M	F
0-39yrs	307	22	15	67	56	18	34	20	75
40-59	342	28	18	89	40	20	32	26	89
60+	223	46	26	37	16	19	21	16	42
Level 1	21	5	0	4	3	2	0	0	7
2	160	13	15	33	22	9	18	4	46
3	229	16	8	58	39	16	31	16	45
4	325	37	19	74	35	23	26	27	84
5	52	10	10	6	2	2	4	9	9
LMM	36	17	12	0	0	1	2	1	3
SSM	460	25	27	111	74	31	47	26	119
NM	177	30	7	40	20	7	17	19	37
ALM	16	1	0	0	0	4	4	5	2
NOS	157	21	11	35	18	13	14	10	35
Other	22	1	2	6	0	1	3	1	8
Local	784	81	53	176	104	55	80	46	189
Regionl	79	12	4	15	7	2	5	15	19
Distant	7	2	0	2	1	1	1	0	0

NOS = not otherwise specified

"Other" refers to borderline melanoma, atypical junctional nevus, blue nevus and unspecified.

Figure 14 over/



**Figure 14**

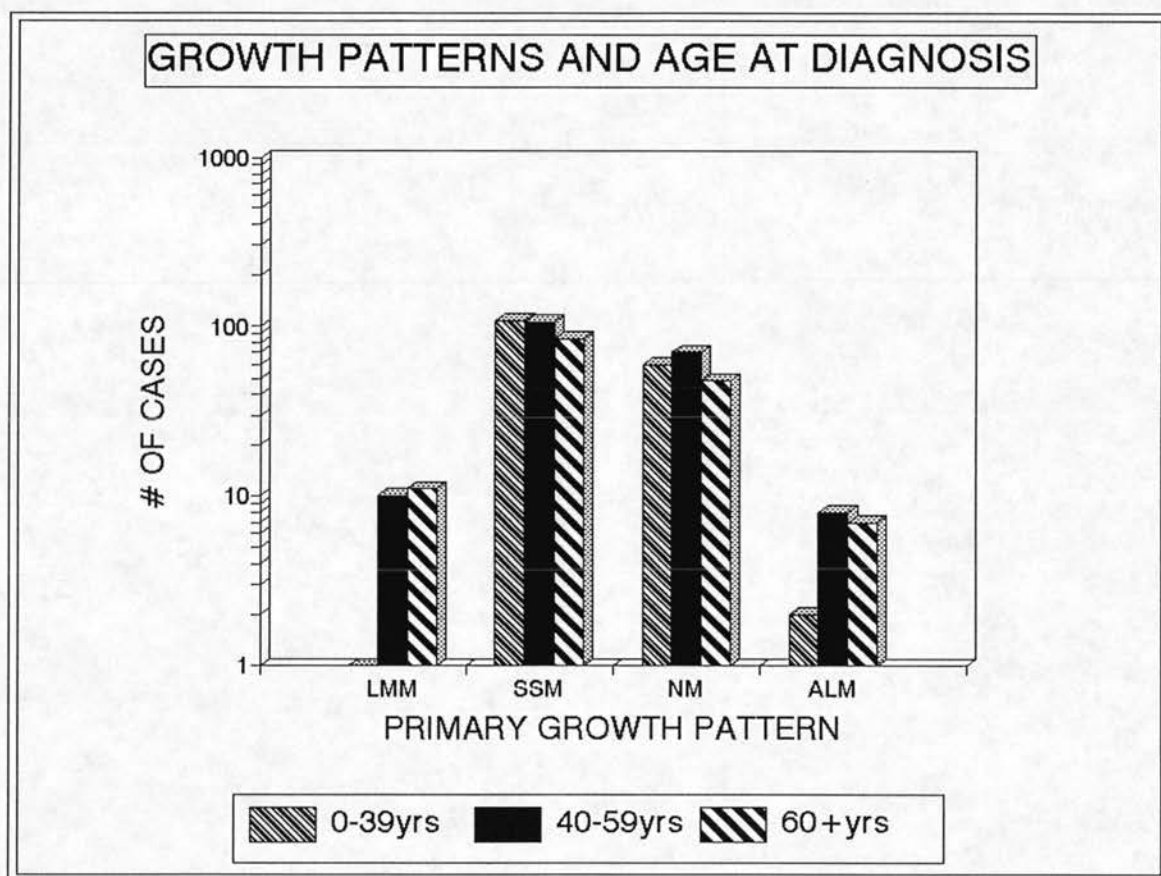
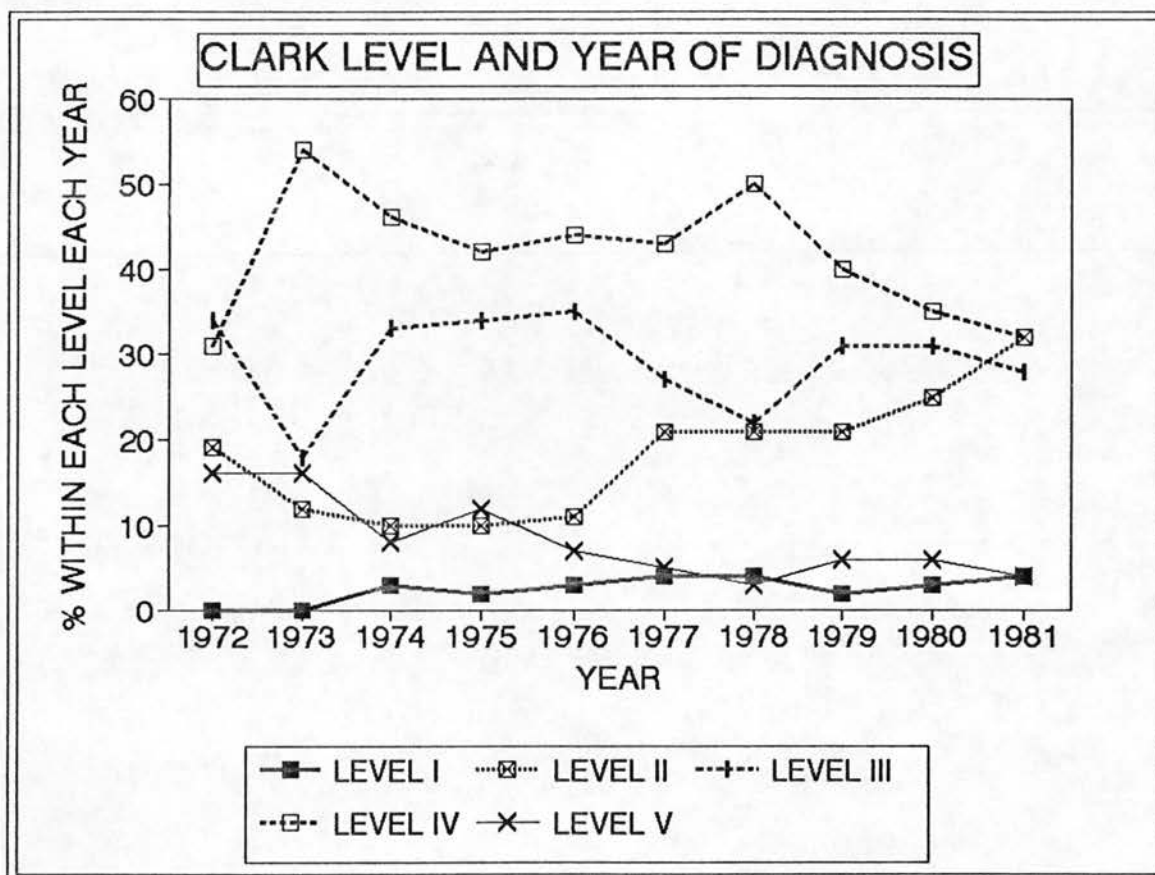


Figure 15



### **3I. Correlation of Pathology with Growth Pattern.**

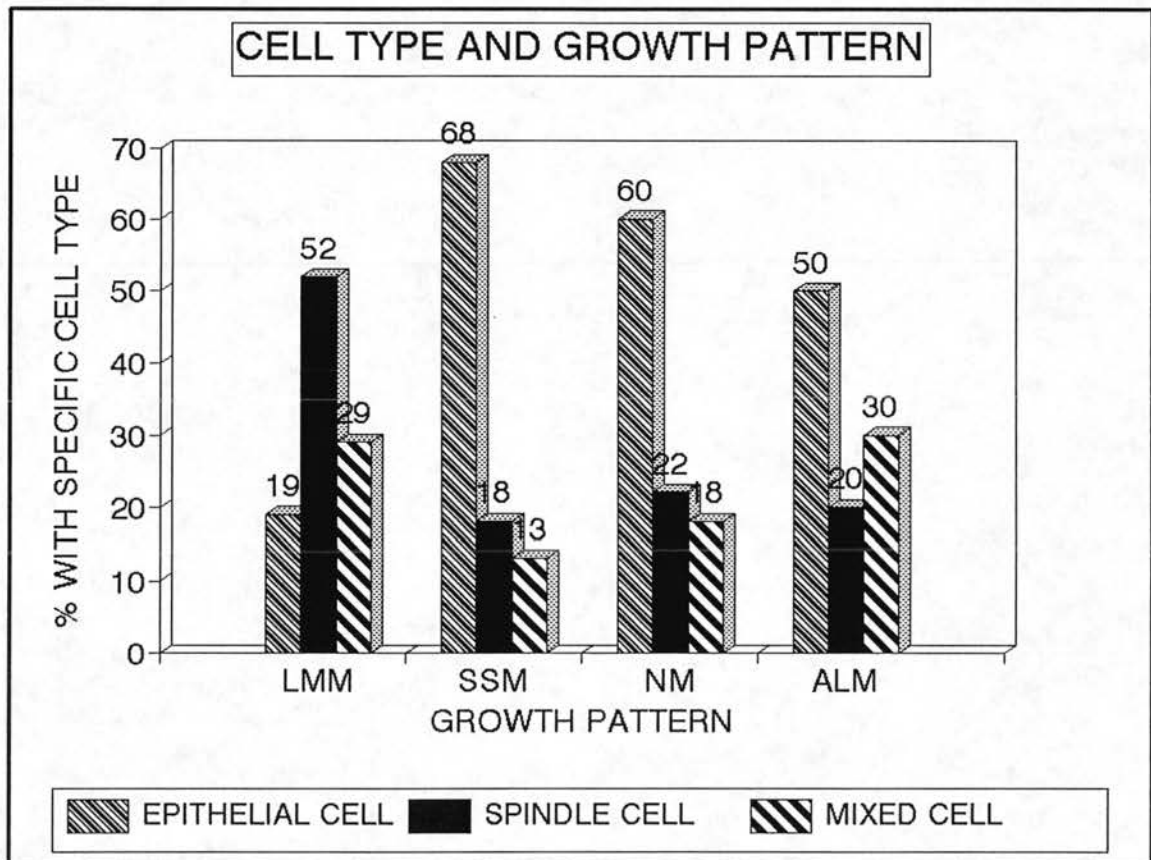
Several pathological correlates were assessed according to primary growth pattern. Dermal or compound nevi were associated with 10% of SSM and 13% of NM. Junctional nevus was associated with 6% of SSM and 4% of NM. Cell type according to growth pattern is shown in Figure 16. Most SSM and NM had epithelial cell type, and LMM had predominantly spindle cell type. Analysis of cell type according to body site showed no significant variations, epithelial cell type accounting for 53-63% and spindle cell 22-26% at all sites.

Degree of differentiation according to growth pattern is summarised in Figure 17. ALM and NM were most commonly poorly differentiated [66% and 46% respectively]. In contrast, only 13% of SSM and 14% of LMM were poorly differentiated.

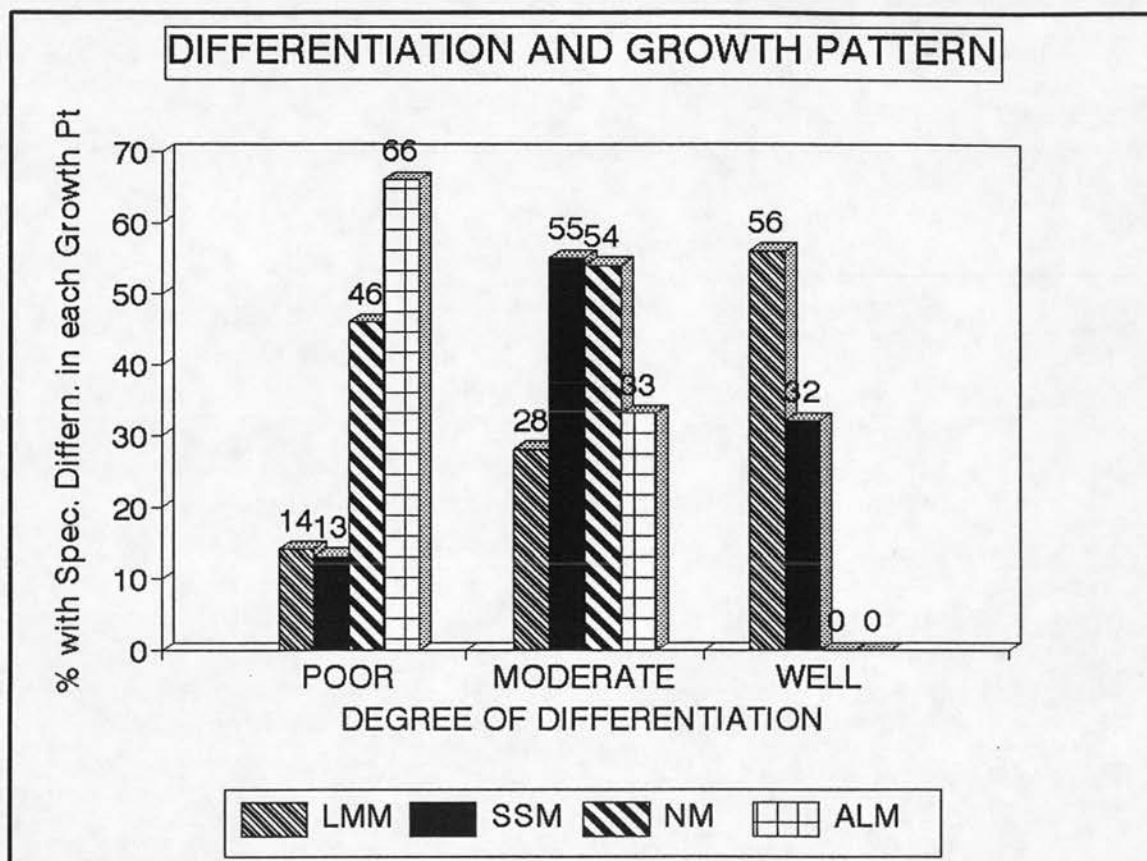
Lymphatic invasion occurred in 10% of NM, 7% of LMM and 4% of SSM. Venous invasion was reported in only 4 cases, 3 [1.7%] NM and 1 [0.2%] SSM. Peri-lymphatic inflammation according to thickness is presented in Figure 18. Overall, it was present in 3.5% of T1 and 2, and 10.5% of T3 and 4 primaries.

Figures 16, 17, 18 over /

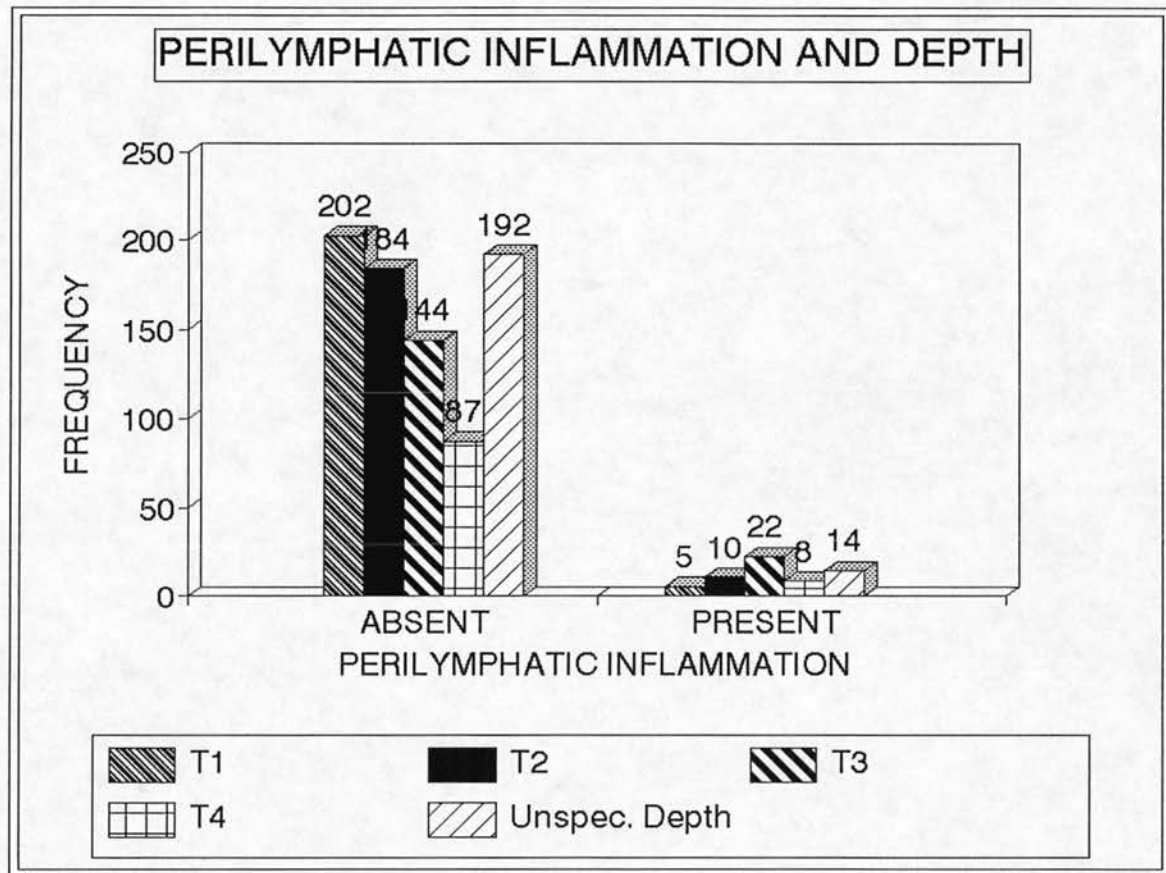
**Figure 16**



**Figure 17**



**Figure 18**





Presence of inflammatory reaction according to primary depth is shown in Figure 19. For T1 primaries, moderate or marked inflammatory reaction was present in 73% of cases whereas in T4 primaries 54% had no or only slight inflammatory reaction.

### **3J. Depth of Invasion, Sex, Primary Site, Growth Pattern and Stage.**

Final Analysis of depth of invasion by sex according to age, primary site, growth pattern and stage is presented in Table 8. There were 223 cases missing from this analysis, mainly because of absence of depth measurement. Overall median depth of invasion was 1.20mm, mean 1.73mm +/- 1.49. Median for females was 1.10mm and for males 1.45mm. The respective means were 1.56mm +/- 1.39 and 1.93 +/- 1.57.

Depth distribution of primary tumors was 31% T1, 29% T2, 25% T3 and 15% T4. Females had 61% of T1, 55% of T2, 52% of T3 and 43% of T4 primaries. Primary tumors T1 and T2 constituted 55% of all H&N, 57% of all LL, 61% of all T and 69% of all UL lesions. By Clark's classification, levels II and III constituted 39% of all H & N, 45% of all LL, 55% of all T and 56% of all UL lesions. Males had 54% of T1 and T2, 56% of level II and III, 69% of T3 and T4 and 62% of levels IV and V H & N primaries. Males had 62% of T1 and T2, 60% levels II and III, and 70% of T3 and T4, 68% levels IV and V trunk primaries. Females had 65% of T1 and T2, 66%

levels II and III, and 62% of T3 and T4, 45% levels IV and V upper limb primaries. Females had 86% of T1 and T2, 85% levels II and III, and 73% of T3 and T4, 72% levels IV and V lower limb primaries.

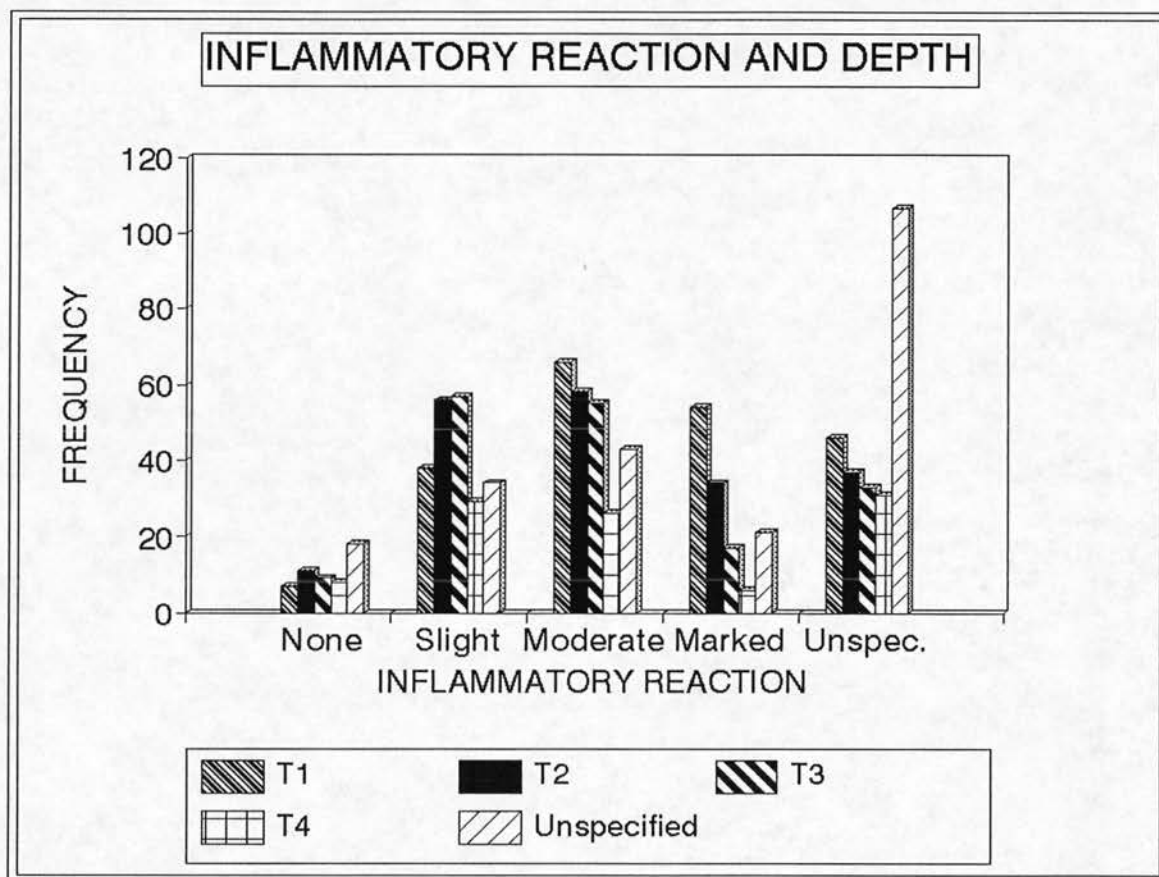
SSM and LMM tended towards thinner lesions : 42% of SSM and 62% of LMM were T1. NM presented with thicker lesions : 46% were T3 and 37% were T4. ALM had an infrequent growth pattern : 66% were T3 and T4.

### **3K. Tumor Depth, Diameter and Volume.**

Tumor measurements of depth, diameter and volume in those cases in whom both were available are presented in Table 9. There was a significant difference in means between the sexes for all measured values. Overall primary median diameter was 10.00mm, mean 13.15mm +/- 10.11. Median diameters were identical for both sexes but depth of invasion and tumor volume were greater in males. Overall median tumor volume was 106 mm<sup>3</sup>, mean 401 mm<sup>3</sup> +/- 1309.8.

Figure 19 over /

**Figure 19**



**Table 8.**

**Final Analysis of all new cases of Cutaneous Malignant Melanoma categorised by Depth and sex, age, primary site, growth pattern and stage. % is of total population of cases with a measured depth of invasion [ 668 cases ].**

	T1	T1	T2	T2	T3	T3	T4	T4
	M	F	M	F	M	F	M	F
0-39	31	54	19	47	33	40	12	11
40-59	31	55	45	37	29	36	20	15
60+	18	19	23	23	19	12	23	16
H&N	17	17	15	10	14	9	19	6
Trunk	45	32	46	24	47	14	19	14
UL	14	28	13	22	8	16	5	5
LL	4	51	13	51	12	49	12	17
LMM	8	8	2	2	1	1	3	1
SSM	65	110	63	75	30	45	12	11
NM	0	1	12	12	33	32	30	22
ALM	1	0	1	2	3	1	2	2
NOS	6	9	9	16	14	9	8	6
Local	80	128	84	105	72	78	44	36
Regnl.	0	0	3	2	9	10	11	6
Distant	0	0	0	0	0	0	0	0

**LMM** = lentigo maligna melanoma

**SSM** = superficial spreading melanoma

**NM** = nodular melanoma

**ALM** = acral-lentiginous melanoma

"Other" refers to borderline melanoma, atypical junctional nevus, metastatic, and not otherwise specified.

**Table 9.**

**Measured Characteristics of Primary Tumor**

	#		Medn		Mean		Std. Dev.	
	M	F	M	F	M	F	M	F
<b>Depth</b>	290	355	1.45	1.1	1.93	1.56	1.57	1.4
<b>Diam.</b>	374	415	10.0	10.0	14.2	12.2	11.2	8.9
<b>Vol.</b>	265	320	148.8	88.4	548.2	279.2	1581	1018

### **3L. Stage.**

Staging information was complete in the Final Analysis in 870 cases : 90% local, 9% regional and 1% distant disease. Regional lymph node dissection was performed in 282 patients and 84 [29.8%] were positive histologically. The incidence of regional or distant disease according to primary site in the total staged population was 6.2% [UL], 7% [T], 11.8% [H & N] and 12.6% [LL], and according to primary site in males and females respectively was 14.7% and 7% [H & N], 8.8% and 7.1% [T], 5.2% and 7% [UL], and 24.6% and 9.1% [LL]. No T1 primaries were spread beyond the local area. Regional metastases occurred in 2.5% of total T2, 11.3% of total T3, and 17.2% of total T4 primaries at presentation.

### **3M. Recurrence.**

Disease recurred in 38% of patients in the Final Analysis. There were 5 cases in whom disease recurred 10 + years from diagnosis. Of all females, 32% experienced recurrence and of males, 44%. Figure 20 shows the distribution of sites of recurrence by primary site. Local recurrence is within 5cm of the primary. "Organ" category includes lungs, liver and brain, and "Other" includes bone, marrow, skin, non-regional nodes and unspecified sites. Of all first recurrences 54% were in regional lymph nodes. Primary sites responsible for all first recurrences were T [38%], LL [25%], H&N [22%] and UL [13%]. First recurrence occurred in a single site



in 46% of patients with recurrence, 27% in 2 sites, 16% in 3 sites and 11% in 4+ sites.

### **3N. Survival.**

Survival in males and females is illustrated in Figure 21. Five, 10 and 15 year survival proportions were 68.9%, 58.2% and 55.5% for males and 82.9%, 74% and 70.3% for females. Overall mean survival times + standard error of those who died from melanoma were 11.3 + 0.36 years for males and 13.78 + 0.3 years for females. Female survival was significantly longer [ $\chi^2 = 27.65$ ;  $p = < 0.00001$ ]. Detailed analysis of prognostic factors is presented in Chapter 3. Melanoma was the cause of death for 31% of patients and accounted for 82% of all deaths. Survival analysis at last follow up is shown in Table 10. Of all patients who had a recurrence, 16% were disease free at last follow up.

### **3O. Other Cancers.**

Other malignancies occurred in 115 [13%] patients following melanoma diagnosis, mostly [66%] non-melanoma skin cancer. Subsequent primary melanoma occurred in 21 [2.2%] patients.

Figures 20, 21 over /

Figure 20

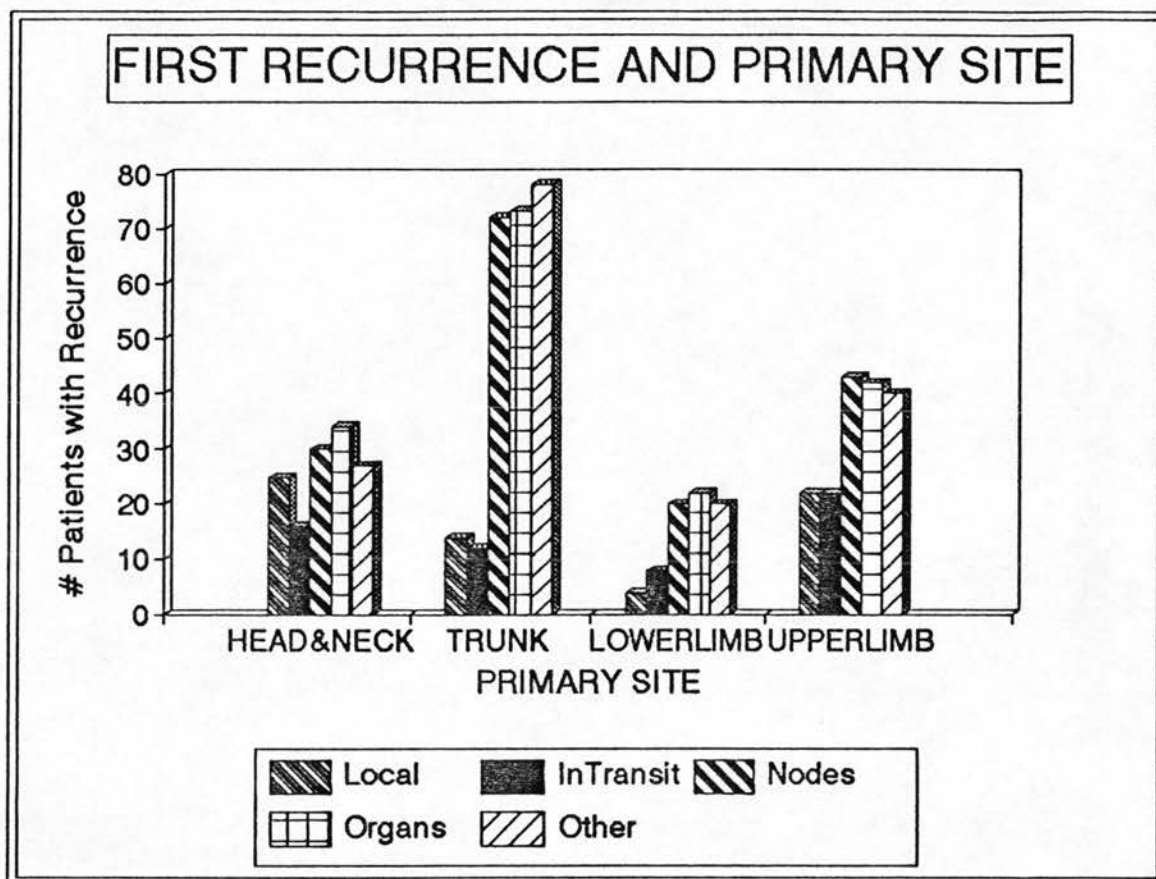
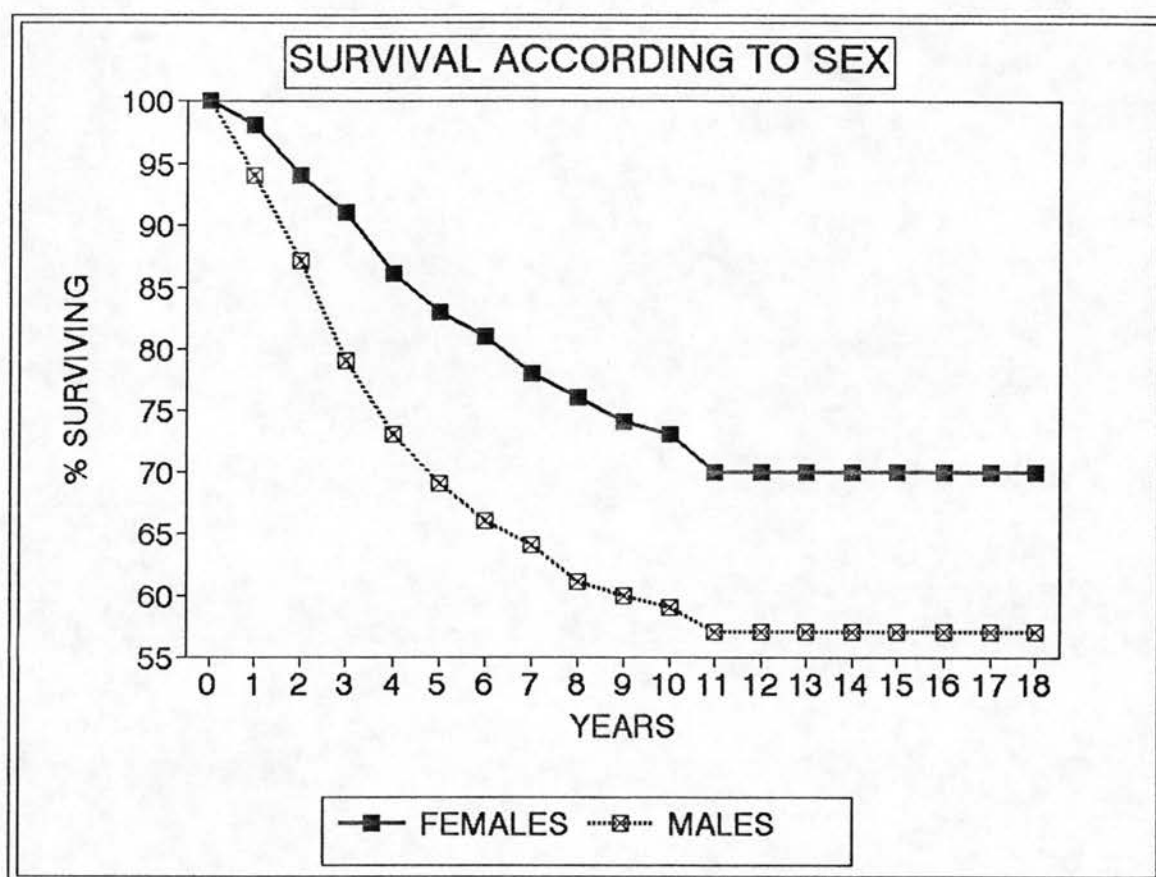


Figure 21



**Table 10.****Survival status at last follow-up**

<b>PATIENT STATUS</b>	<b># PTS.</b>	<b>% STUDY POPULATION</b>
Alive, disease free since primary treatment	465	52.3
Dead from disease	280	31.4
Alive, disease free since treatment for recurrence	54	6.1
Dead from other causes, disease absent	52	5.8
Lost to follow up	11	1.2
Dead from other causes, disease present	10	1.1
Dead from other causes, disease status unknown	8	0.9
Alive, disease present from recurrence after disease free interval	8	0.9
Alive, current disease status unknown	2	0.2
Alive, disease present continuously since diagnosis	1	0.1

## **4. DISCUSSION**

### **4A. Epidemiology.**

Cutaneous malignant melanoma has been studied extensively over the past 20 years, seeking better understanding of demographic, environmental, clinical and pathological factors. The increase in age-standardised incidence in western developed countries has been well documented [Roush, Holford, Schymura et al., 1987 : Muir and Nectoux, 1982 : Osterlind, Engholm, Jensen, 1988] and a similar pattern was seen in this study. Melanoma incidence in several countries has increased by 5% per annum in the 1960's and 70's [Magnus, 1977]. These increasing rates suggest that the trends observed are the results of true changes in risk.

Comparisons of the incidence of melanoma are difficult because of different dates of reports and the known progressive increase in incidence in many parts of the world [Balch and Milton, 1985]. The 1988 incidence rates in men [11.5] and women [12.8] in BC are certainly lower than Australia [20.4 and 24.5 per 100,000 for men and women, in 1976] and higher than Scotland [5.1 per 100,000 in 1979]. In Sweden the incidence of melanoma has risen from 2.5 to 11.6 per 100,000 in 1980. Melanoma incidence in BC is therefore intermediate in relative world terms but its

progressive increase is cause for serious concern.

Although melanoma prognosis is improving, the rising incidence is associated with an annual increase in death rate of 3% per year in North America [Gallagher and McBride, 1987]. Data from the Surveillance, Epidemiology and End-Results program [Ries, Hankey, Edwards, 1990] show that the incidence in males exceeds that in females and is increasing at a faster rate [4.8% per year compared with 3.6%]; the death rates in males and females are increasing at 2.5% and 1.3% a year respectively. In this present study, the death rate in males has exceeded that in females in 8 of the 9 years from 1977-85 and overall survival for males was shorter for new patients registered from 1972-81.

Median age [47 years] of all patients in this study was virtually the same as those reported from Sydney and Alabama [48 and 44 years respectively] [Balch, Shaw, Soong et al., 1985]. The only age at which there was a striking sex difference was in the 4th decade when females had 66% of all melanomas. This was due to the 4.3 fold increase in female lower limb melanoma incidence which was evident at all ages.

#### **4B. Second Melanoma Risk.**

Melanoma patients have an increased risk of subsequent melanoma.



The magnitude of risk is 3-5% [Bellet, Vaisman, Mastrangelo et al., 1977 : Lynch, Frichot, Lynch et al., 1975 : Moseley, Giuliano, Storm et al., 1979]. The observation of previous and subsequent melanoma rates of 1.4% and 2.8% in this series is consistent with these previous reports. The risk of second melanoma is considerably higher than the risk of developing first melanoma in the general population. In the USA, the lifetime risk of developing one melanoma is about 0.15% [Roses, Harris, Ackerman, 1983]. Patients with previous melanoma require surveillance for new primary disease as well as for recurrent disease.

#### **4C. Nevi and Melanoma.**

The association of cutaneous nevi and melanoma has been known for many years. Firstly, the existence of above-average numbers of nevi has been reported to be a significant risk factor [Lee, 1985 : Swerdlow, English, Mackie et al., 1986]. Secondly, individuals with giant congenital nevi have a risk of up to 8% [Kopf, Bart, Rodriguez-Sains, 1977]. Thirdly, histologic sections of melanomas often show associated pre-existing intradermal nevi, occurring in up to 40% of melanomas [McGovern, 1972]. Finally, some individuals and family members have peculiar-looking nevi which are dysplastic histologically and which have a significant likelihood of becoming malignant [Greene, Clark, Tucker et al, 1985]. The relationship between nevi and melanoma is discussed further in the Chapter 1.

In the present series, almost 20% of patients had a previous benign mole removed. The study period antedated the description of the dysplastic nevus syndrome and it is not possible to relate the melanomas to these abnormal nevi. The medical records were insufficient to determine the incidence of moles, normal or abnormal, in the patients' immediate family. However, co-existent nevi of any type were reported pathologically in only 13.9% of cases of established melanoma. This rate is less than in many reports but slightly higher than previously described [Clark, Ainsworth, Bernardino et al., 1969].

#### **4D. Presenting Symptoms.**

Growth and color change were the main presenting symptoms [total 65%] and this is in accordance with previous reports in which these symptoms occurred in over 70% of new melanoma patients [Milton and Lewis, 1963 : Wick, Sober, Fitzpatrick et al, 1980]. Analysis of distribution of presenting symptoms by primary site showed fewest bleeding/ulcerated lesions on the upper limb and more head and neck lesions presenting with development of a new mole. Fifteen percent of LMM, 8% of SSM and 3% of NM were recognised incidentally by physicians. Alternatively stated, patients complained of 97% of NM, 92% of SSM and 85% of LMM. There did not appear to be undue delay in NM diagnosis with more NM being diagnosed within a year of symptoms than SSM. Itching in a mole is a

suspicious symptom [Milton, 1968 : Wick, Sober, Fitzpatrick et al., 1980 : Mackie, 1990]. In the present series , itching was more common in NM [15%] than in SSM [6%].

#### **4E. Symptom Duration.**

A median symptom duration of 5.9 months was almost the same as reported from the Sydney Melanoma Unit [5 months] where females had a slightly longer symptom duration than males [6.2 vs. 4.5 months]. This could be interpreted as an indicator of biologically less aggressive tumors since longer symptomatic periods are associated with long natural history in other tumors eg. gastric cancer [Rains and Capper, 1968]. Observations of longer intervals to recurrence in females and that a statistically significant survival advantage was demonstrated only in those dying with melanoma would be also be consistent with females having biologically less aggressive tumors. In a study of melanomas of 3 depth groups [ $<0.75\text{mm}$ ,  $0.75\text{-}3\text{mm}$ ,  $>3\text{mm}$ ], symptom duration was not longer in thick compared to thin melanomas [Hersey, Sillar, Howe et al., 1991], suggesting that thicker tumors have a more rapid growth rate. Thick tumors were mainly nodular melanomas of the head and neck in older males.

#### **4F. Primary Diameter.**

At diagnosis, 49% of tumors were under 1 cm in diameter but over

the decade there was no indication that the primary diagnosis was being made earlier judging by primary diameter. In contrast however, the proportion of Clark level 1 and 2 primaries has increased in that time. This is more important because tumor depth is a much more significant prognostic factor than diameter [Drzewiecki and Andersen, 1982].

#### **4G. Biopsy and Definitive Primary Surgery.**

Excision and incision biopsy techniques are usually recommended for diagnostic purposes [Urist, Balch, Milton, 1985] and these accounted for 98.5% of all biopsies in the present series. Specifically, shave biopsies are not recommended and only one was performed in this series. The optimum width of excision as definitive management of primary melanoma remains debatable. The risk of local recurrence is determined more by the depth of the primary than the width of normal skin excised around it [Urist, Balch, Milton, 1985]. A trend towards recommending narrower excision margins than the classical 5cm all round has occurred in the 1980's, and a large co-operative group trial in North America is currently investigating a 2 versus 4 cm excision margin [US Intergroup Melanoma Trial]. During the period of the present study, there was no decrease in the number of >5cm excisions undertaken as primary treatment. An excision of >1cm skin was undertaken in 89-94% of patients with measured tumor depth T1-4 but wider excisions [>5cm skin] were performed in a smaller proportion

[57-74%]. Recurrence data have not been analysed according to width of excision.

#### **4H. Histopathology.**

The principal histopathological features of primary melanoma are growth pattern, tumor thickness and depth of invasion, ulceration, cell type, mitotic activity, lymphocytic reaction. cell type, vascular invasion, regression, pigmentation, associated pre-existing nevi and solar degeneration [McGovern and Murad, 1985]. Both the extent of definitive surgery and assessment of individual prognosis are based upon histopathology. However, agreement between pathologists about various histologic parameters other than thickness is only about 70% [Larsen, Little, Orell et al., 1980]. Furthermore, the prognostic usefulness of specific histopathologic features depends on the criteria used to test such variables as ulceration, mitoses and lymphocyte response [Day, Harrist, Gorstein et al., 1981 : Day, Sober, Lew et al., 1981 : Day, Lew, Mihm et al., 1982]. In the present study, over half of the pathology slides were reviewed centrally and this could certainly influence conclusions about histopathological features. For example, cell type, differentiation and mitotic rate were frequently unspecified in type or degree.

#### **4Hi. Differentiation.**

Differentiation in the primary was related to growth pattern, bad prognosis growth pattern being associated with less well differentiated tumors. Specifically, nodular and acral-lentiginous melanoma were virtually never well-differentiated, and historically these types are more likely to recur than SSM or LMM [Balch, Soong, Shaw et al., 1985].

#### **4Hii. Lymphatic and Vascular Invasion.**

Lymphatic and vascular invasion were infrequent, especially venous invasion [4 cases]. Vascular invasion rates in previous reports varied from 0.7% [Little, 1972], 5.8% [Larsen and Grude, 1979] to 37% [Hornstein and Weidner, 1973]. The wide variation in these reported rates suggests either under-reporting or over-reporting. Many studies have reported however that vascular invasion is an adverse prognostic factor [Ronan, Han, Das Gupta, 1988], but other studies have not [Sondergaard and Schou, 1985].

#### **4Hiii. Inflammatory Reactions.**

Inflammatory reactions were commoner in association with thinner primary tumors but specific perilymphatic inflammation was commoner with thicker primaries. There is no uniformity in reporting host response in terms of inflammatory reaction in melanoma and this has led to difficulty in evaluating its significance [Ronan, Han, Das Gupta, 1988]. Detailed



analysis of histological features will be discussed in the context of prognostic factor analysis [Chapter 3].

#### **4I. Comparison of Various World Series.**

##### **4Hi. Sex Ratio and Age.**

Data on sex, age, primary site and growth patterns have been compared with the findings of 12 other major series from the USA [Griffel, 1974 : Fisher, 1989 : Newell, Sider, Bergfelt et al., 1988 : Popescu, Beard, Treacy et al., 1990 : Balch, Urist, Maddox et al, 1985], Canada [McGregor, Birdell, Grace et al., 1983], New Zealand [Shaw, 1988], Scotland [Pondes, Hunter, White et al., 1981 : Mackie and Hunter, 1982], Ireland [Gordon and Lowry, 1986], Denmark [Osterlind, Hou-Jensen, Jensen, 1988] and Australia [McCarthy, Shaw, Milton et al., 1985]. This study's sex ratio was similar to all series except those of Ireland and two in Scotland where the female : male ratios were 2.8, 1.9 and 2.17 : 1 respectively. All series except two in the USA [Fisher, 1989 : Newell, Sider, Bergfelt et al., 1988] showed a female preponderance. Median ages of patients in this study were slightly lower than most others reported.

##### **4Iii. Primary Site.**

The commonest primary site in females in all studies is the lower

limb accounting for 33-67% of all cutaneous melanoma. For males, the trunk was the commonest primary site [33-47%] in all studies except Ireland, Scotland and Rochester where head and neck was the commonest site. The findings in this study that 46% of all male melanomas were located on the trunk and 44% of all female melanomas were on the lower limb are consistent with most other series. A trend of increasing frequency of trunk melanoma and decreasing frequency of head and neck melanoma in males has been reported from Sydney and Alabama [Balch, Shaw, Soong et al., 1985] in the period 1958-85. Unfortunately, at the time this study was initiated, ICDO disease site codes did not distinguish distal from proximal extremity, although BCCA has now incorporated sub-site distinctions into its present melanoma staging diagram. Lesions on the feet have previously been associated with poorer prognosis [Balch, Soong, Shaw et al., 1985] : similarly, scalp lesions had poorer survival than face or neck primaries.

#### **4liii. Primary Growth Pattern.**

In this study, the observed growth pattern distribution was consistent with most previous reports. The most frequent [65%] growth pattern was superficial spreading melanoma, with nodular melanoma and lentigo malignant melanoma accounting for 25% and 5% respectively. SSM is usually the most common growth pattern [51-73%] nodular melanoma next

[14-35%] with lentigo malignant melanoma between 4-9%. In Ireland, nodular melanoma was the most common type and lentigo malignant melanoma caused 18% of all melanomas [Gordon and Lowry, 1986].

#### **4liv. Depth of Invasion.**

Depth measurement by micrometer is now accepted as the most important indicator of prognosis [Balch, Soong, Shaw et al., 1985]. The observations that 61% of the total population had primary tumors less than 1.5mm depth and that no T1 primaries were spread beyond the local area at diagnosis provide both encouragement and incentive to increase educational efforts towards earlier recognition and diagnosis. Depth comparisons with other series are hindered by lack of standard reporting practices. In the south-east Scotland series from 1971-76, only 30% of patients had T1 and 2 tumors [Pondes, Hunter, White et al., 1981]. In a worldwide comparative study [Balch, Soong, Shaw, 1985], 12% of patients had primary tumors >4mm thick whereas in this series 15% were >3.0mm. In the combined experience of the Sydney Melanoma Group and the University of Alabama, median tumor thickness for males and females has decreased since the 1950's [Balch, Shaw, Soong et al., 1985] to 1.4 and 1.2mm during 1976-80. These are close to the median depths observed from 1972-81 in the present series [1.45mm for males and 1.10mm for females]. Poorer prognosis in nodular melanoma [Balch, Soong, Shaw et

al., 1985] is related to their depth. For example, 83% of NM but only 24% of SSM were T3 or T4 in this series. ALM is also usually a deep lesion [66% were T3 or T4].

#### **4lv. Depth of Invasion and Clark Level.**

Observed correlations between frequencies of micrometer depths and Clark levels varied from excellent [in female lower limb primaries] to fair [T1 and T2 primaries in all body sites in both sexes]. The distribution of tumor thickness within each Clark level is similar to previous reports [Balch, Murad, Soong et al., 1979]. The prognostic separation which each staging system permits will be studied further.

#### **4J. Tumor Volume.**

Estimation of tumor volume is potentially flawed by concomitant non-invasive components in the primary contributing to greater diameter and volume. However, in a large series such as this it may be valid. Median tumor diameters were found to be identical for both males and females. Tumor volume was greater than expected in males from depth alone. This may have been due to the absence of either depth or diameter measurements in some patients leading to a larger difference between the sexes.

#### **4K. Stage.**

Several staging systems have been utilised in malignant melanoma [Ghussen, Kruger, Groth, 1990]. The original 3 stage system of local [stage 1], regional [stage 2] and distant [stage 3], and the MD Anderson Hospital system used here are purely anatomical, whereas the American Joint Committee and the International Union Against Cancer systems incorporate depth of the primary in the definition of different stages. The elective lymph node dissection rate in various series obviously influences eventual stage but this factor is not included in any of the staging systems except when it is positive with consequent up-staging. Most series report that the majority of patients have stage 1 disease at presentation, consistent with this series. Correlating primary sites with potential metastatic disease at diagnosis according to sex showed that males had about twice the likelihood of regional or metastatic disease with head and neck primaries compared with females and almost three times with lower limb primaries. Elective and therapeutic lymph node dissection analyses will be reported separately.

#### **4L. Recurrence.**

The pattern of recurrent disease in melanoma is now well known. The disease free interval is directly related to the depth of the primary [Balch and Milton, 1985]. Regional lymph nodes are the commonest site

of first metastasis. In this series, 54% of first recurrences were in regional nodes. In a recent series of 377 stage 1 patients, 100 of whom underwent elective lymph node dissection [ELND], 43% of first recurrences were in regional lymph nodes and 57% were in distant sites [Meyskens, Berdeaux, Parks et al., 1988]. ELND is known to be associated with a different pattern of metastatic disease ie. fewer regional nodal metastases [down from about 60% to 5%] and proportionate increase in other sites [McCarthy, Shaw, Milton, 1985]. The expected likelihood and pattern of metastases influences follow-up recommendations with thinner lesions requiring less vigorous attention than thick tumors [McCarthy, Shaw, Thompson et al., 1988]. The distribution of distant metastases in the present series is consistent with previous reports. The prognostic significance of developing recurrent disease is very clear from this series. Only 16% of patients experiencing recurrence were free of disease at last follow-up. New treatments are urgently required for this group of patients.

The phenomenon of late recurrence in melanoma is well known, particularly in choroidal melanoma. In the present series, there were 5 recurrences 10+ years after diagnosis. In a series of 105 stage 1 cutaneous melanoma patients, there were 7 recurrences beyond 10 years [Briele, Beattie, Ronan et al., 1983], and at that time there had been 7 other reports in the literature. In a series of 536 patients, 5 had late



recurrence [Callaway and Briggs, 1989], and in a series of 769 patients, there were 11 cases of late recurrence [McEwan, Smith, Matthews, 1990]. These events are important from the point of view of necessity for clinical and statistical follow-up. The estimated late recurrence rate among those patients who survive the first 10 years after diagnosis is 7% [McEwan, Smith, Matthews et al., 1990].

#### **4M. Prognosis in Males.**

Poorer prognosis of malignant melanoma in males is well documented [Balch, Shaw, Soong et al., 1985 : O'Doherty, Prescott, White et al., 1986] and confirmed here. Male sex has been shown to be an independently poor prognostic factor. The sex difference in survival in the present study could be due to several factors. Males had thicker and larger volume tumors in general, predilection to trunk, head and neck primaries, the majority of thick primaries in these sites, the majority of regional or metastatic disease in all sites except upper limb at presentation and a tendency to shorter disease-free intervals to recurrence.

The role of hormonal factors in the etiology and natural history of malignant melanoma has been recognised and investigated for over 40 years. Early reports of a therapeutic effect of orchidectomy [Herbst, 1943 : Howes, 1943] stimulated interest in endocrine aspects of melanoma which

was intensified with the demonstration of steroid hormone receptor proteins in melanoma in the 1970's [Fisher, Neifeld, Lippman, 1976]. Practically however, the observed single agent response rates in metastatic melanoma to estrogens, anti-estrogens, androgens, progestogens and glucocorticoids have been disappointingly low [Walker, 1988 : Rose, Pedersen, Mouridsen, 1985] and it remains to be shown that hormonal mechanisms can be used to advantage in the treatment of melanoma.

There has been renewed interest recently in anti-estrogen therapy in metastatic melanoma in conjunction with chemotherapy since a higher than expected response rate was observed in patients treated with tamoxifen, BCNU, Cisplatin and DTIC [De Prete, Maurer, O'Donnell et al., 1984]. The effect of tamoxifen may however be to increase the sensitivity of melanoma cells to cisplatin [McClay, Albright, Jones et al., 1991]. A randomised trial to determine the contribution of tamoxifen to these chemotherapy agents is now underway in the USA.

#### **4N. Comparison of Outcomes Between Series.**

Several factors must be taken into account when comparing survival of patients between series [Balch, Soong, Shaw, 1985]. Referral centre results differ from population-based studies. Results from the last decade may be superior due to earlier diagnosis. The distribution of tumor

thickness must be considered. Patterns of surgical practice, especially the elective lymph node dissection rate, will have a significant effect on staging and possibly on ultimate survival. Relapse is less likely in pathological compared to clinical stage 1 patients. In this series, overall 5-year survivals of 68.9% and 82.9% for males and females [10% of whom had regional or distant metastases at diagnosis] compare favorably with those from 11 series in which 5-year survivals for stage 1 melanoma ranged from 62-81% and 70-100% in males and females respectively.

#### **40. Future Prospects.**

Early diagnosis is the best available method of improving survival in cutaneous malignant melanoma. Since CMM can be found readily by self inspection, there is an opportunity to shorten median times to diagnosis with education. A public health education program in Queensland resulted in more thin tumors registered recently compared to 10 years previously [Little, Holt, Davis, 1980]. An increased proportion of thin melanomas has also been reported following public and physician education campaigns in United Kingdom [O'Doherty and Mackie, 1988 ; Fairris, 1988 : Curley, Marsden, Fallarfield et al., 1988 : Mackie, 1990 : Harris and Savin, 1990]. A physician checklist of **major** [changes in size, shape and color] and **minor** [inflammation, bleeding/crusting, sensory change, diameter > 7mm] features suspicious of melanoma formed the basis of the successful

campaign for early diagnosis of melanoma in the west of Scotland [Mackie, 1990]. It has been suggested that further campaigns be directed towards high risk individuals identified by risk factor charts rather than whole populations [Mackie, Freudenberger, Aitchison, 1989 : Harris and Savin, 1990]. Warning signs in a mole, assymetry, border irregularity, color variation, and diameter [ $>6\text{mm}$ ], known as the **ABCD of melanoma** [Friedman and Rigel, 1985], have been emphasised along with assessment and surveillance of individuals with dysplastic nevus syndrome and/or family members with melanoma [Reynold and Austin, 1984]. Public campaigns and further research in early detection and treatment should be capable of reducing melanoma mortality, especially in areas of higher incidence such as British Columbia.

## **CHAPTER 3**

**ANALYSIS OF**

**PROGNOSTIC FACTORS**

**IN**

**CLINICAL STAGE 1**

**MALIGNANT MELANOMA**



## **1. INTRODUCTION.**

- A. General.
- B. Methods of risk factor analysis.
- C. Literature review.
- D. Prognostic factors and staging systems.
- E. Present study.

## **2. PATIENTS AND METHODS.**

- A. Patient population.
- B. Data collection.
- C. Definition of factors.
- D. Statistical methods.

## **3. RESULTS.**

- A. Univariate analysis.
- B. Multivariate analysis.
- C. Survival proportions.

#### **4. DISCUSSION.**

- A. Methodological issues.
- B. Single factor results.
- C. Multivariate analysis results.
- D. Prognostic index.
- E. Prognostic factors and staging systems.
- F. Level and depth interactions.
- G. Primary sites.
- H. Age.
- I. Growth pattern.
- J. Primary ulceration.
- K. Other factors.
- L. Conclusions.

## **1. INTRODUCTION**

### **1A. General.**

The clinical behaviour of malignant melanoma can be quite variable. The phenomena of recurrence of melanoma thought likely curable and the lack of further recurrence in some patients who have already experienced recurrence are familiar to clinicians following melanoma patients. The likelihood or risk of recurrence after surgery for stage 1 primary melanoma can however be assessed with reasonable accuracy in most patients. Several developments in contemporary understanding of malignant melanoma now allow clinicians to offer patients a good estimate of the chance of recurrence. This is not only helpful to patients but is of major importance in undertaking studies of adjuvant therapy and in comparing results of treatment in different centres.

The principal elements of the third and contemporary period of melanoma history are the description of four primary growth patterns and the recognition that depth of the invasive component is the major determinant of survival [Clark, Ainsworth, Bernardino et al., 1969 : Breslow, 1970 : Reed, 1976]. The first report of depth of invasion as a prognostic factor was in 1953 [Allen and Spitz, 1953].

## **1B. Methodological issues.**

Three approaches have been used to study relations between single factors in survival analysis after initial treatment. These include direct numerical relations [graphics, cross-tabulations, chi-square tests], stratification of variables, and multivariate analysis. The latter was chosen to study significant factors from univariate analysis in the present report. This permits accurate identification of the dominant risk factor(s). For example, survival in female lower extremity melanoma is generally good : whether this relates to patient sex, primary site, primary growth pattern , primary depth or other factors can be assessed by multifactorial analysis.

The Cox proportional hazards model is currently the preferred method of survival analysis throughout the world [Cox, 1972 : Lew, Day, Harrist et al., 1983]. This analysis selects from a list of single factors the "best" combination to predict survival. A stepwise procedure forcing single factors and combinations to compete is undertaken. The best individual prognostic factors are selected and complementary factors are added one at a time to complete the model. The model selects factors associated with earlier as opposed to late death. Data with dominance of short-term follow-up may yield different conclusions from more mature data. Alternative models should be routinely formed to examine other possible contributing factors [Day, Lew, Mihm et al., 1982]. Potentially important

factors should be tested in different ways, such as Clark level being examined as a dichotomous variable [ie level II v. other levels, levels II and III v. levels IV and V, level V v others] and as a linear variable [ie level II = 1, level III = 2 etc.]. Most programs undertaking the Cox model exclude all patients in a series with even one piece of relevant data missing. If such exclusions are > 10% of the patients there is a risk of selection bias. At completion of the model, results should be confirmed by life-table survival analysis.

The Cox proportional hazards model is ideal for assessing time to recurrence or death. In contrast, logistic regression analysis is ideal for binary events [events which have two possible outcomes], and can be expanded to include more than two possible outcomes, such as categorical variables [Vollmer, 1989].

### **1C. Literature review.**

Prognostic factor analyses have been reported by many groups and institutions. The Universities of Alabama and Sydney have reported the largest collaborative study of prognostic factors for primary, regional and metastatic melanoma [Balch, Soong, Shaw et al., 1985]. In 3505 stage 1 patients, principal characteristics were as follows : median age 45 years, 53% female, 27% T1, 30% T2 primaries, 24% ulcerated. Single factor

survival analysis showed female sex, extremity compared with axial primary, increasing age, tumor thickness, level of invasion, ulceration, regression, pigmentation [all  $p < 0.00001$ ], growth pattern [LMM and SSM > NM,  $p < 0.0004$ ], lymphocytic infiltration [ $p < 0.0066$ ], highly significant. Further analysis of primary site showed scalp to be worse than other head and neck primary sites [ $p < 0.05$ ] and foot to be worse than other lower extremity sites [ $p < 0.00001$ ]. The poorer prognosis of scalp along with upper back, upper outer arm and neck [BANS] primaries had been reported previously [Day, Mihm, Lew et al., 1982] but this study did not confirm the BANS sites as high risk. Females had better survival in all extremity sub-sites [ $p < 0.00001$ ] but had similar survival with head, neck and trunk primaries. Males had more frequent ulceration of the primary [29 vs 19%] and this could contribute to their poorer prognosis. Between the sexes there was no difference in survival with ulcerated primaries. Elective lymph node dissection [ELND] was of borderline significance [ $p = 0.069$ ]. Prognosis of acral-lentiginous melanoma [ALM] was not assessed because of its relatively recent recognition and the importance of minimum 8-10 years follow-up.

The significant single factors which were still significant in multifactorial analysis were thickness, ELND, pathological stage [1 vs 3], ulceration and primary site [all  $p < 0.00001$ ], while level of invasion, sex



and regression were significant to a lesser degree. Thickness and ulceration had the best correlation with survival in all subgroups examined. Unlike the other significant prognostic factors, ELND was non-random in distribution ie patients were selected to have this procedure. It is therefore possible that the selection process identified a specific risk group rather than the procedure having survival benefit.

Stage 3 and 4 [MD Anderson system] patients were also examined for prognostic features. Stage 3 patients were grouped as 3B1 and 3B2, and 3B3, 3B4. Single factor analysis showed primary ulceration to be most significant [ $p < 0.00001$ ] followed by number of nodes positive [ $p < 0.0002$ ], thickness [ $p < 0.004$ ] and age [ $p < 0.0369$ ]. Multifactorial analysis showed only number of nodes [ $p < 0.0005$ ], ulceration [ $p < 0.00001$ ] and age [ $p < 0.0478$ ] to be significant : tumor thickness was of marginal significance [ $p = 0.0686$ ]. Survival of the 3 groups within stage 3 was similar provided it was calculated from time of lymph node metastases. For patients with distant metastases, number of metastatic sites and location of metastases were significant in both uni- and multivariate analysis and remission duration was also significant in the multifactorial model.

Multivariate and discriminant analyses have been undertaken to define 4 risk groups of patients with stage 1 melanoma [Schmoeckel,

Bockelbrink, Bockelbrink et al, 1983 and 1983]. In 585 cases, the most significant factors were tumor depth and mitotic activity, particularly when combined as a "**prognostic index**". Vascular invasion, ulceration in tumors >3mm thick, severe cellular atypia, small lymphocyte-like cell type and absence of inflammatory response were also associated with high risk of metastases. Less relevant factors were level of invasion, sex, site, tumor breadth, and clinical diameters. Growth pattern, age, symptom duration, presence of co-existing nevus were not significant risk factors for recurrence. Using the significant factors, a classification of melanoma into 4 risk groups was developed :

1. **Low Risk** : <8% recurrence rate.

Features : <0.75mm thick + mitotic index <10 mit/mm<sup>2</sup> :

no signs of regression, ulceration, vascular invasion : cases with diameter >3cm should be classified as medium risk.

2. **Medium Risk** : approximately 30% recurrence rate.

Features : cases other than low, high or very high risk.

3. **High Risk** : approximately 65% recurrence rate.

Features : prognostic index >13: or ulceration in tumors >3mm thick.

4. **Very High Risk** : approximately 95% recurrence rate.

Features : mitotic index >25mit/mm<sup>2</sup> : or unequivocal vascular invasion : or high risk melanoma in palmar, plantar or subungual location.

#### **1D. Prognostic factors and staging systems.**

Because of their prognostic implications, depth and level of invasion have been incorporated into the current melanoma staging systems of the International Union Against Cancer [UICC] and the American Joint Committee on Cancer [AJCC] {Ghussen, Kruger, Groth, 1990}.

**UICC stages** are summarised ;

Stage 1 ; local primary  $\leq 1.50\text{mm}$ , level  $\leq 3$ .

Stage 2 ; " " 1.51-4.00mm, level 4

Stage 3 ; " "  $>4.00\text{mm}$ , level 5 or satellites, or in transit metastases or regional node metastases.

Stage 4 ; distant metastases.

**AJCC stages** are summarised ;

Stage 1A ; local primary  $\leq 0.75\text{mm}$ , level  $\leq 2$

Stage 1B ; " " 0.76-1.50mm, level 3

Stage 2A ; " " 1.51-4.00mm, level 4

Stage 2B ; " "  $>4.00\text{mm}$ , level 5 or satellites

Stage 3 ; Regional nodes, mobile and  $<5\text{cm}$  diameter, or  $<5$  in transit mets.

Stage 4 ; Regional nodes,  $>5\text{cm}$  diam, or  $>5$  in transit mets. or distant mets.

In an analysis of 220 patients with extremity primary melanoma treated by wide primary excision, regional node dissection and limb perfusion these staging systems have been compared with the original 3 stage system and the MD Anderson system, which do not take account of depth or level of invasion [Ghussen, Kruger, Groth, 1990]. The AJCC system provided best differentiation of prognosis. Differences in survival between stages were stage 1 and 2 [ $p=0.078$ ], stage 2 and 3 [ $p<0.001$ ], stage 3 and 4 [ $p<0.001$ ], stage 2A and 2B [ $p<0.001$ ]. There were only 9 stage 1A patients and the difference in survival between stage 1A and 1B [31 patients] was not significant [ $p=0.4$ ].

#### **1E. Present study.**

The present study is a retrospective review of cutaneous malignant melanoma registered with the British Columbia Cancer Agency [BCCA] between 1972 and 1981. Clinical and pathologic factors previously reported to be of prognostic significance have been identified from the patients' clinical records and analysed according to outcome with a minimum follow-up of 7.9 years. For treatment purposes during this time, melanomas were classified as low or high risk. Primary depth was used to distinguish the two groups. Up to 1982, lesions less than 0.75 mm deep were classified low risk. Since 1982, lesions more than 1.5 mm thick have been classified high risk. The extent of primary surgery [width of excision and

ELND] and inclusion in adjuvant trials depend on the low/high risk classification. Stage was defined using the MD Anderson Hospital system.

The present study is the first analysis of outcome in these patients. Clinical and pathological descriptions varied in completeness. For example, primary tumor depth measurements were unavailable in 223 cases. Most of the histologic sections were reviewed by 2 BCCA pathologists. Most of the clinical descriptions of the primary tumor were obtained from medical records prior to consultation at BCCA since most patients had the primary removed prior to referral. These descriptions were from many family physicians, dermatologists and general surgeons, with varying completeness.

## **2. PATIENTS AND METHODS**

### **2A. Patient population.**

In 1983 a retrospective review of all patients registered in the BCCA with malignant melanoma from June 1 1972 to May 31 1981 was commenced. Full details of the patient population and reasons for exclusion are described in Chapter 2 [Carmichael and Wilson, 1991]. In summary, 1944 patients were registered with malignant melanoma in the Provincial Cancer Registry, 1245 of whom were referred to the BCCA. Final analysis was undertaken on 891 patients.

## **2B. Data collection.**

A Chart Abstract Form was completed from each patient's chart from which the following clinical and pathological factors were analysed:

### **1. Clinical**

Age at diagnosis, sex, primary site, diameter, color, surface elevation, ulceration, regression, extent of initial surgery, stage.

### **2. Pathological**

- a. growth pattern : lentigo malignant melanoma [LMM], superficial spreading melanoma [SSM], nodular melanoma [NM]. acral-lentiginous melanoma [ALM ], not otherwise specified [NOS]
- b. mitotic rate : low [1/5 high power fields]  
moderate [1/5 - 1/hpf]  
high [>1/hpf]
- c. polypoid configuration : absent / present
- d. regression : absent / present
- e. ulceration : absent / present
- f. degree of pigmentation : none/minimal/moderate/marked  
unspecified degree / unspecified
- g. Clark level of invasion : I, II, III, IV, V ; micrometer depth in mms.
- h. lymphatic / vascular invasion : absent / present
- i. dominant cell type : epithelioid/spindle/mixed/other/unspecified
- j. degree of differentiation : poor/moderate/well/unspecified



- k. associated nevus : absent / present
- l. presence and degree of inflammatory reaction :  
absent / present : slight / moderate / marked / unspecified
- m. presence of perilymphatic inflammation : absent / present
- n. stage : MD Anderson system

A total of 796 patients were identified with stage 1 disease. Clark level 1 patients and those with "borderline melanoma" were excluded from analysis because of 100% survival. Follow-up data was missing in 7 cases leaving a total of 753 cases for analysis.

## **2C. Definition of factors.**

Age refers to age at pathological diagnosis. Age was treated as a continuous variable for the multivariate analysis and as a categorical variable for univariate analysis. Categorisation of age was determined by partitioning melanoma mortality distribution.

Histopathology was performed in hospitals throughout the province, most slides being reviewed by two pathologists in the BCCA. Tumor growth patterns and depth were reported using standard criteria [Clark, Ainsworth, Bernardino et al., 1969 : Clark, 1967 : Breslow, 1970]. Depth categorisation was determined from the **T** category of the TNM classification [American

Cancer Society, 1983] : T1 <0.75mm, T2 0.76-1.50mm, T3 1.51-3.00mm, and T4 >3.0mm. Depth was used as a categorical variable in univariate analysis and as a continuous covariate in its logarithmic form for multivariate analysis. Tumor volume was calculated from :

$$V = \pi * [\text{diameter} / 2]^2 * \text{depth}.$$

Mitotic rate was assessed in 5 high power fields for each primary tumor. Mitotic rate was treated as a categorical variable for both forms of analysis since no actual counts of mitoses per square mm. were recorded.

**BANS** sites refer to primary tumor located on the following parts of the body surface : upper back, posterior aspect of upper arms, posterior neck and scalp. The posterior upper arm was not coded separately in the Chart Abstract Form. This report utilises posterior upper extremity instead.

## **2D. Statistical methods.**

The principal study objective was evaluation of survival from melanoma in relation to various clinical and pathological factors. The response variable was time from diagnosis to death from melanoma. Observation times for patients leaving the study for reasons other than death from melanoma, and for patients alive at last follow-up were considered as censored observations. Survival times were calculated from

date of diagnosis to date of death or last physician contact. Cases with missing data were excluded from the relevant analysis procedure.

Univariate analysis was performed to assess the prognostic value for survival of individual variables using the product limit method [Kaplan and Meier, 1958] with a biomedical computer program BMDP [version 1988]. The log rank test was used to determine significance of differences between categories [Peto, Pike, Armitage et al., 1977].

Multivariate analysis was undertaken with the Cox regression model [Cox, 1972] using Harrell's program PHGLM written for SAS. Significant co-variables, determined through univariate analysis, were initially entered into the model and a continuous stepwise analysis was performed. Different combinations of covariates and alternative models were examined to determine the best prognostic model.

The PHGLM program solves the non-linear equation with iterative techniques. Analysis and computation are easier if there is one failure or death from melanoma in each time period [Vollmer, 1989]. Coding of factors in the regression model is critical [Vollmer, 1989]. Linear relationships implying a decrease in prognosis may not hold for certain covariates, as each category within a covariate may have a distinct

biological effect. The categories in Clark level, growth patterns, inflammatory reaction, surface description and primary site have been coded as separate binary factors. These covariates have been analysed both in a binary and linear manner for multivariate analysis. The proportional hazards assumption in the final model was checked graphically [Andersen, 1982].

Three methods of calculation of survival proportions were used : disease-specific, disease-free and overall. Disease-specific survival is calculated using only those patients who died from melanoma. Overall survival proportions are calculated using deaths from all causes. Disease-free survival refers to time from diagnosis to first recurrence.

### **3. RESULTS**

#### **3A. Univariate analysis.**

Univariate analysis results and log rank test p values are presented in Table 1. Date of diagnosis, sex, primary site including BANS sites, growth pattern, surface description, Clark level, depth of invasion, clinical and pathological ulceration, tumor diameter and volume, lymphatic invasion, mitotic rate, inflammatory reaction, invasion to stratum corneum, pigmentation, polypoid configuration and type of surgery were significant. There were insufficient cases of LMM with adequate data to assess its

prognostic significance. Age, primary color, type of inflammatory infiltrate, primary cell type, clinical and pathological regression, previous nevi were not significant.

### **3B. Multivariate analysis.**

Multivariate model building was applied to various groupings of covariates in order to find a scoring of the variables that gave rise to a satisfactory proportional hazards model. The full model shown in Table 2 had a total of 217 cases of which 54 were uncensored. A total of 543 cases were deleted due to absence of one or more covariate values. As no more than 10% of the number of uncensored cases of covariates should be examined in multivariate analysis [Harrell, 1983], different models were examined excluding covariates with a large number of missing values. The reduced model examined 15 covariates with 134 uncensored cases and 120 cases with missing values.

Depth of invasion was coded in logarithmic form to increase the power of the model. Both pigmentation and surface description were found significant in multivariate analysis but were excluded from the final model due to their subjective determination.

**Table 1. Coding and univariate analysis of prognostic factors.**

Factor	# Pts	Uncensd. cases	Missing values	Multivariate Analysis scoring	X <sup>2</sup> , p values from univariate analysis
<b>Clark Level</b>		192	61		
ii	147			1 if lev ii, 0 if not	X = 106.7
iii	219			1 if lev iii, 0 if not	p <0.0001
iv	294			1 if lev iv, 0 if not	
v	32			1 if lev v, 0 if not	
<b>Depth of invasion</b>		160	142		
T1	183			Continuous	X = 97.5
T2	186			( log depth )	p <0.0001
T3	156				
T4	86				
<b>Pathol Ulceration</b>		209	16		
-	544			0 if absent	X = 66.9
+	193			1 if present	p <0.0001
<b>Growth Pattern</b>		215	24		
SSM	428			1 if SSM, 0 if not	
NM	153			1 if NM, 0 if not	X = 40.4
ALM	13			1 if ALM, 0 if not	p <0.0001
NOS	135			0 if NOS	
<b>Tumor Volume</b>		143	208		
<300mm <sup>3</sup>	405			continuous	X = 35.7
300-600mm <sup>3</sup>	67				p <0.0001
600-900mm <sup>3</sup>	22				
>900mm <sup>3</sup>	51				
<b>Clinical ulceration</b>		193	52		
-	529			0 if absent	X = 33.6
+	172			1 if present	p <0.0001
<b>Date of Diagnosis</b>		218	0		
<1978	420			0 if <1978	X = 27.8
1978 +	333			1 if 1978 +	p <0.0001
<b>Gender</b>		218	0		
Male	347			0 if male	X = 24.5
Female	406			1 if female	p <0.0001
<b>Lymphatic Invasion</b>		204	17		
-	702			0 if absent	X = 22.2
+	34			1 if present	p <0.0001



Table 1 cont.

Factor	# Pts.	Uncens. cases	Missing Values	Multivariate anal. scoring	X <sup>2</sup> , p values from univar. analysis
<b>Surface descrpn.</b>		183	135		
Flat	159			1 if flat, 0 if not	X = 23.3
Raised	396			1 if raised, 0 if not	p <0.0001
Both	63			0 if both	
<b>Prim. Site</b>		218	0		
Head & Neck	123			1 if H&N, 0 if not	X = 20.9
Trunk	274			1 if trunk, 0 if not	p <0.0001
Upper Limb	133			1 if UL, 0 if not	
Lower Limb	223			0 if LL	
<b>Inflam. Reaction</b>		150	183		
Slight	192			1 if slight, 0 if not	
Moderate	225			1 if moderate, 0 if not	
Marked	117			1 if marked, 0 if not	
None	36			0 if none	
<b>Pigmentn.</b>		203	32		
Minimal	127				X = 18.4
Moderate	168			1 if moderate, 0 if not	p 0.0011
Marked	153			1 if marked, 0 if not	
Unspec.	273			0 if minimal	
<b>Tumor Diam.</b>		199	75		
<5mm	107			continuous	X = 13.7
6-8mm	123				p 0.0052
9-10mm	141				
11-15mm	157				
16+mm	150				
<b>BANS Sites</b>		218	0		
Absent	548			0 if absent	X = 12.5
Present	205			1 if present	p 0.0004

Table 1 cont.

Factor	# Pts	Uncens pts	Missing values	Multivar. anal. score	X <sup>2</sup> , p values (univ anal.)
<b>Mitoses</b>		133	303		
Low	175			1 (low), 0 if not	X = 12.8
Medium	185			1 (medium), 0 if not	p 0.0017
High	90			0 if high	
<b>Color</b>		172	155		
None	2				X = 13.7
Black	122				p 0.0565
Blue	26				
Red	30				
Brown	326				
Grey	84				
White	8				
<b>Surgery</b>		217	33		
Local Excision	192			1 if LE, 0 if not	X = 11.2
LE + ELND	3			1 if LE + ELND, 0 if not	p 0.0472
Wide Excision	327			1 if WE, 0 if not	
WE + ELND	198			0 if WE + ELND	
<b>Polypoid</b>		213	6		
Absent	686			0 if absent	X = 9.4
Present	61			1 if present	p 0.0022
<b>Cell Type</b>		110	418		
Epithelioid	199				X = 5.2
Spindle	81				p 0.1595
Mixed	55				
<b>Age</b>		218	0		
0-39	272				X = 3.95
40-59	301				p 0.1391
60+	180				
<b>Str Corn inv</b>		211	15		
-	369			0 if absent	X = 8.5
+	379			1 if present	p 0.003
<b>Previous nevi</b>		218	0		
-	714				X = 0.21
+	39				p 0.6436

When the covariates coded in a binary manner in the reduced model in Table 2 were assessed in the final model, several covariates became significant. All the Clark level and growth pattern covariates became significant with beta values of -1.98, -1.36 and -0.92 for Clark levels II, III and IV respectively and beta values of 0.96, 0.80 and 1.44 for SSM, NM and ALM respectively.

Alternate models coding primary site as head and neck, anterior trunk, posterior trunk and extremities were examined. The final models differed from the reported model in Table 2 in that BANS sites and sex were significant and other primary sites were not. When the model was adjusted for Clark level, significant factors were BANS sites, sex and lymphatic invasion.

When the analysis was commenced, surface description and pigmentation were both included in all the reduced models because they were significant. The final model included the covariates for raised surfaces and moderate pigmentation for all models with the exception of the model adjusted for log depth. In this model, only raised surface was significant. Because of the subjective determination of these covariates, they were eliminated from the reported reduced model.

Date of diagnosis is another covariate that was eliminated from the reported reduced model even though it was significant in all reduced models analysed. This was done because of possible effects of referral patterns contributing to the increase in frequency of thin tumors in the second 5 years of study.

The reduced model covariates were analysed with linear categorical coding instead of binary coding and the results are shown in Table 3. Lymphatic invasion, BANS sites, Clark level and growth pattern were added to the final model as shown in Table 2.

Multivariate analysis was used to determine whether covariates were significantly related to survival after adjusting for the effect of depth of invasion and Clark level. The results are summarised in Table 4. Ulceration and type of initial surgery were significant in all models. When depth adjustment was made, sex, BANS sites and lymphatic invasion replaced primary sites in the final model. When depth was removed, Clark level became highly significant, indicating a high correlation between the two variables.

Tables 2, 3, 4, 5, Figures 1-5 over /

**Table 2. Summary of multivariate analyses with significant prognostic factors.**

	Full model 217 cases		Reduced model 556 cases		Final model 556 cases	
Clark level	Beta	P Value	Beta	p Value	Beta	p Value
ii	-2.5219	0.0499	-1.985	0.0016		
iii	-2.8475	0.0084	-1.356	0.0050		
iv	-2.3975	0.0145	-0.9206	0.0303		
v						
Log Depth	2.6561	0.0024	1.6753	<0.0001	2.0581	<0.0001
Path Ulcer	1.7931	0.007	0.5798	0.0025	0.5912	0.0018
Growth Pattern						
SSM	2.3653	0.0029	0.9552	0.0060		
NM	1.5043	0.0687	0.8006	0.0173		
ALM	2.7067	0.0801	1.4423	0.0203		
NOS						
Tumor Volume	-0.0006	0.282				
Clin Ulcer	-1.3358	0.036				
Lymphatic Invasn	0.6029	0.4383	0.7459	0.0173		
Type of Surgery						
LE	0.9245	0.0515	0.7888	0.0017	0.561	0.0071
LE + ELND	-1.6446	0.0466	0.2431	0.5578		
WE	0.1538	0.7205	0.1635	0.4706		
WE + ELND						
Date of Diagnosis	-0.6838	0.0981				
Gender	-0.500	0.1742				
Age	-0.0055	0.6263				
Primary Site						
Head & Neck	1.8611	0.0037	0.9516	0.0013	0.8782	0.0006
Trunk	1.5978	0.0177	1.1541	<0.0001	0.8985	<0.0001
Upper Limb	1.2882	0.0585	0.3211	0.3269		
Lower Limb						
Tumor Diameter	0.0516	0.2093				
BANS Sites	0.4060	0.3842				
Polypoid configuration	0.7622	0.1724				
Invasion to stratum corneum	-0.7310	0.0867				

**Table 3. Summary of multivariate analysis using linear coding for categorical variates.**

<b>Covariate</b>	<b>Beta</b>	<b>X<sup>2</sup></b>	<b>P value</b>
<b>Log Depth</b>	1.71	22.58	<0.0001
<b>Primary Site</b>	-0.297	10.67	0.0011
<b>Path Ulceration</b>	0.698	13.77	0.0002
<b>Type of Surgery</b>	-0.196	10.13	0.0015
<b>Growth Pattern</b>	-0.208	6.68	0.0097
<b>Clark Level</b>	0.468	7.83	0.0051
<b>BANS Sites</b>	0.471	5.85	0.0159
<b>Lymphatic Invasion</b>	0.632	4.26	0.0389

Survival proportions are presented in Table 5. There were 218 melanoma deaths and 56 deaths from other causes. Overall survival range was 0.23-17.42 years, mean 8.69, median 8.08 years. Survival proportions according to depth of invasion, Clark level, primary ulceration, age at diagnosis and growth pattern are shown graphically in Figures 1 - 5.



**Table 4.**  
**Multivariate analysis**  
**adjusting for Log Depth and Clark Level.**

Significant covariates after adjusting for:

Covariate	Log Depth 645 cases	Clark Level 565 cases	Neither 565 cases
<i>Log Depth</i>		<0.0001	<0.0001
<i>Clark Level</i> II	<0.0001		
III	<0.0001		
IV	<0.02		
V			
<i>Ulceration</i>	<0.0001	0.001	0.002
<i>H&amp;N</i>			
<i>Primary Site</i>		0.0002	0.0006
<i>Trunk</i>		<0.0001	<0.0001
<i>Upper L</i>			
<i>Lower L</i>			
<i>BANS sites</i>	0.0002		
<i>Lymphatic invasn.</i>	0.03		
<i>LE</i>	0.002	0.003	0.007
<i>Surgery</i>			
<i>LE+LND</i>			
<i>WE</i>			
<i>WE+LND</i>			
<i>Sex</i>	0.01		

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*Growth pattern was insignificant in all analyses*

**Table 5. SURVIVAL PROPORTIONS**

	<b>5 yr DFS</b>	<b>Overall 5yr</b>	<b>D/Spec 5yr</b>	<b>D/S 10yr</b>
Level 2	79%	86%	87%	78%
3	66%	81%	87%	78%
4	47%	68%	73%	58%
5	22%	34%	36%	26%
T1	82%	89%	95%	93%
T2	65%	82%	88%	75%
T3	46%	70%	74%	58%
T4	31%	49%	55%	42%
Path ulcer	36%	55%	61%	48%
P/ulcer neg	66%	80%	86%	78%
SSM	68%	80%	87%	78%
NM	44%	59%	66%	52%
ALM	23%	62%	69%	43%
NOS	46%	70%	74%	62%
Male	50%	66%	72%	60%
Female	64%	80%	86%	77%
Lymph Inv+	26%	44%	49%	34%
Lymph Inv-	60%	76%	82%	72%
Surface flat	70%	78%	87%	84%
Raised	50%	69%	74%	62%
Flat+Raised	67%	84%	89%	77%

Table 5 continued. **SURVIVAL PROPORTIONS**

	<b>5 yr DFS</b>	<b>Overall 5yr</b>	<b>D/Spec 5yr</b>	<b>D/S 10yr</b>
Head & Neck	52%	67%	74%	63%
Trunk	51%	68%	73%	62%
Upper Limb	66%	80%	85%	77%
Lower Limb	64%	80%	86%	77%
Min.Pigmtn.	47%	66%	73%	56%
Moderate P.	53%	71%	75%	62%
Marked P.	66%	79%	86%	75%
Unspec P.	63%	77%	83%	76%
Epithel. cells	53%	71%	75%	63%
Spindle cells	62%	77%	85%	73%
Mixed cells	58%	76%	78%	62%
BANS Sites-	61%	76%	82%	73%
BANS Sites+	51%	67%	73%	60%
Mitoses low	66%	81%	88%	78%
Mitoses med.	58%	73%	72%	64%
Mit. frequent	57%	69%	73%	57%
<i>Type of surgery</i>				
LE	51%	68%	67%	38%
LE+ELND	33%	100%	50%	50%

Table 5 contd.

**SURVIVAL PROPORTIONS**

<i>Type of Surgery</i>	<b>5 yr DFS</b>	<b>Overall 5yr</b>	<b>D/Spec 5yr</b>	<b>D/S 10yr</b>
WE	59%	76%	78%	67%
WE+ELND	64%	76%	82%	67%
<i>Polypoid</i>				
Absent	60%	75%	81%	71%
Present	41%	66%	68%	51%
<i>Age Groups</i>				
0-39 yrs	63%	78%	83%	73%
40-59 yrs	58%	75%	79%	68%
60+ yrs	49%	66%	75%	64%
<i>Regression</i>				
Absent	58%	75%	79%	69%
Present	62%	70%	81%	79%
<i>Diagnosis Date</i>				
<1978	49%	70%	74%	61%
>1978	69%	78%	87%	81%

Figure 1

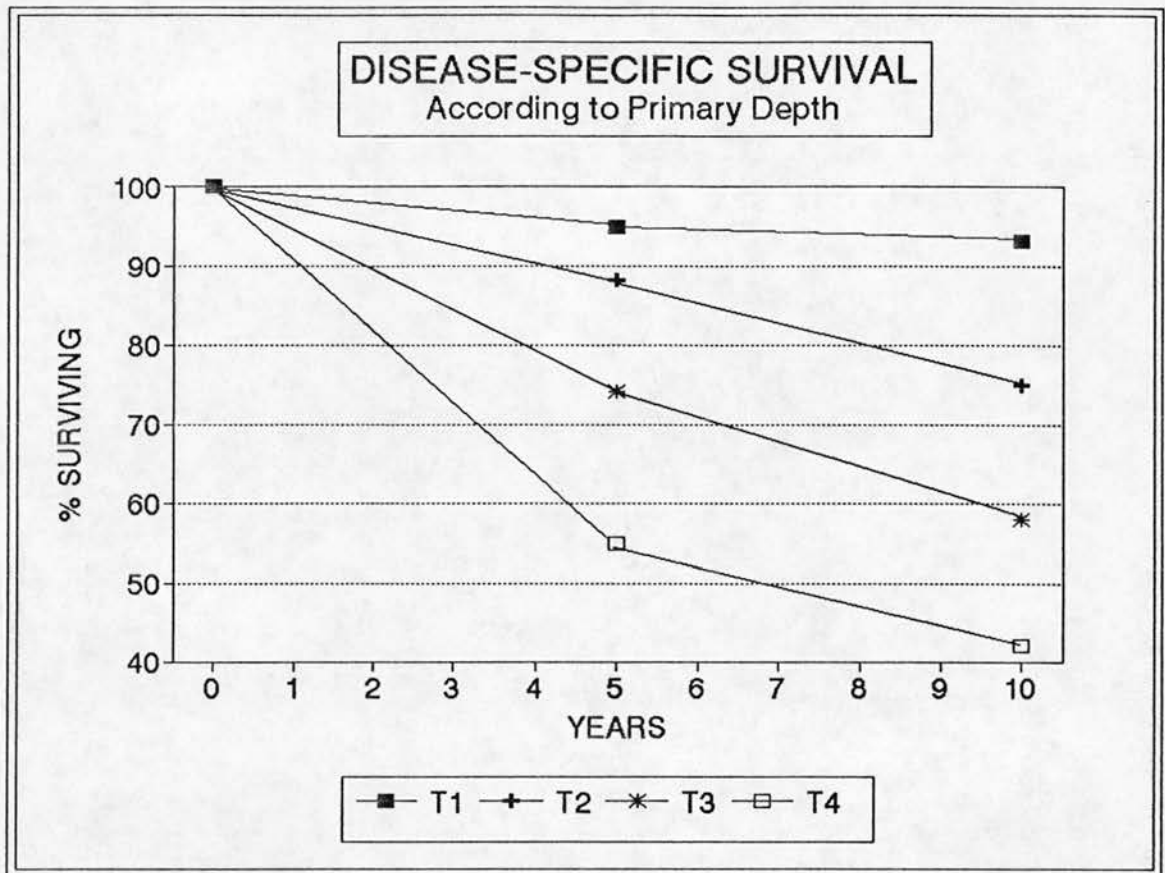


Figure 2

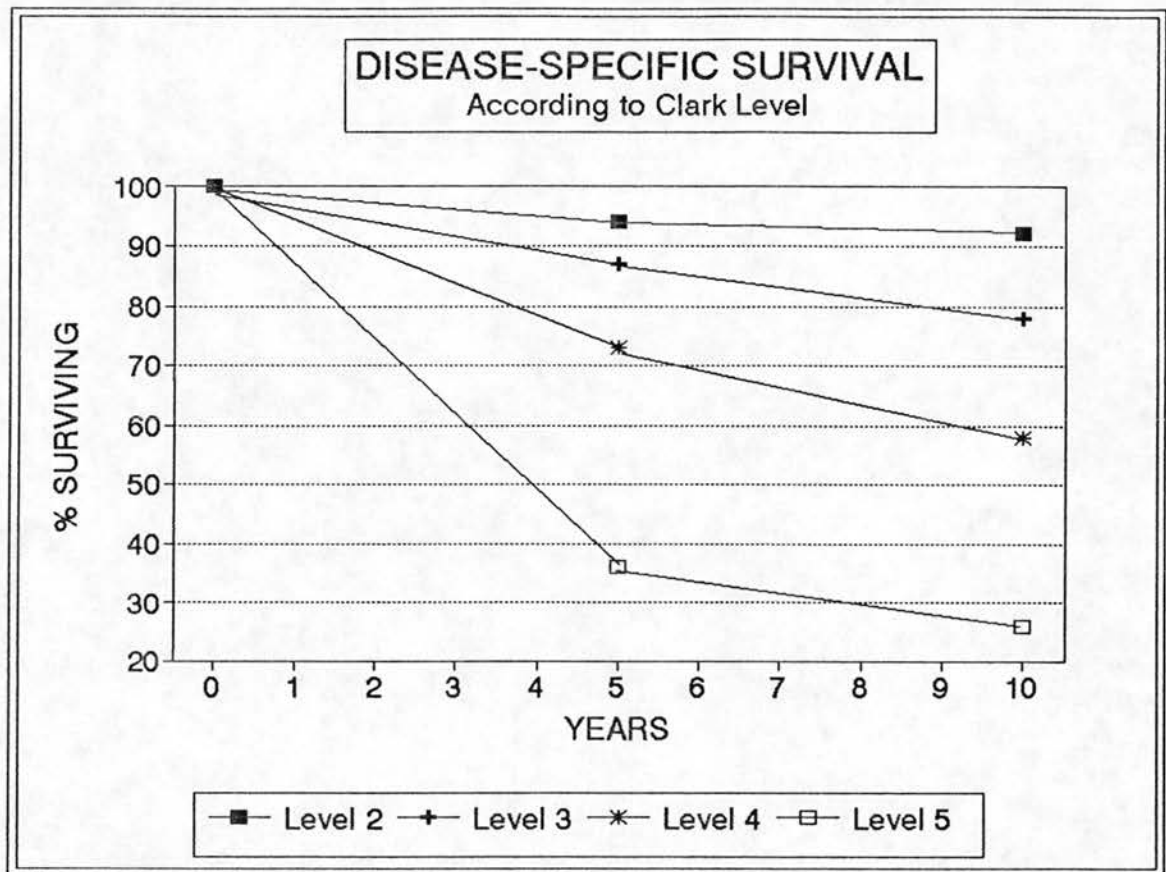




Figure 3

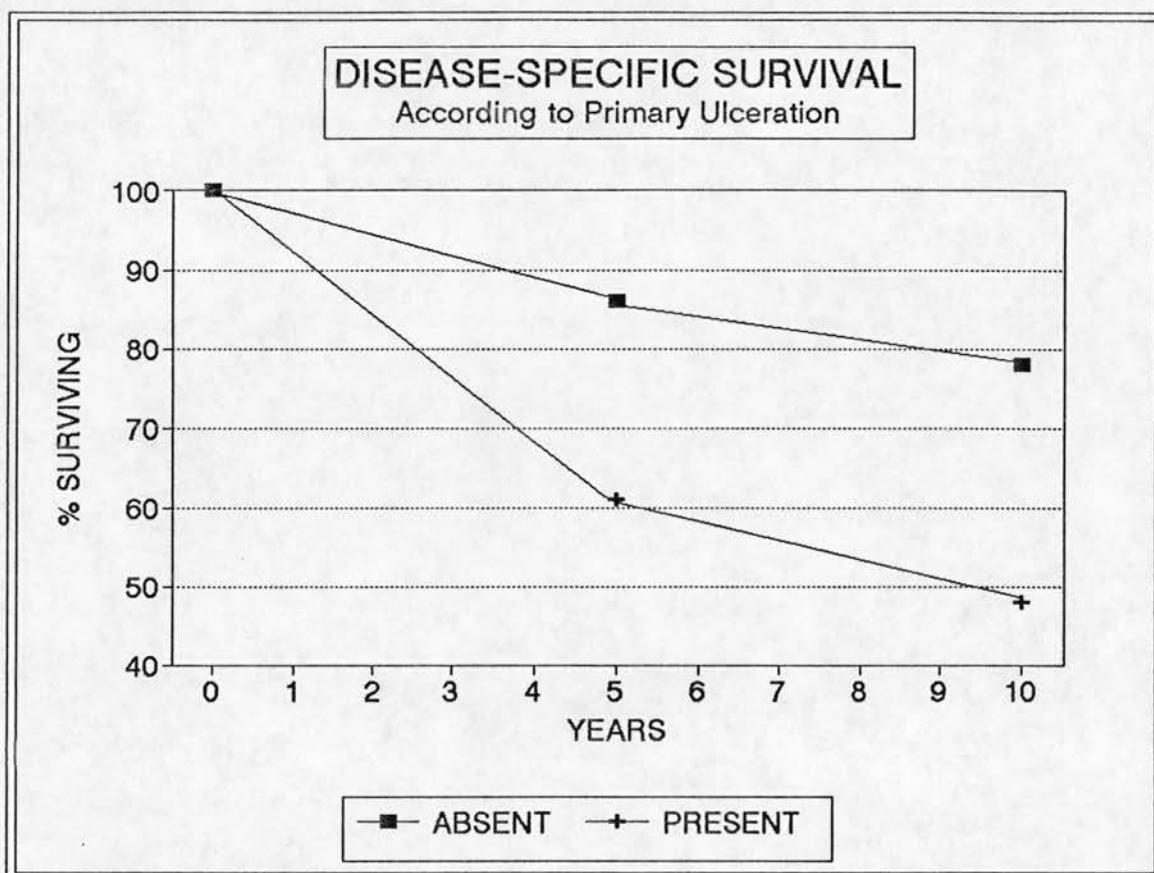


Figure 4

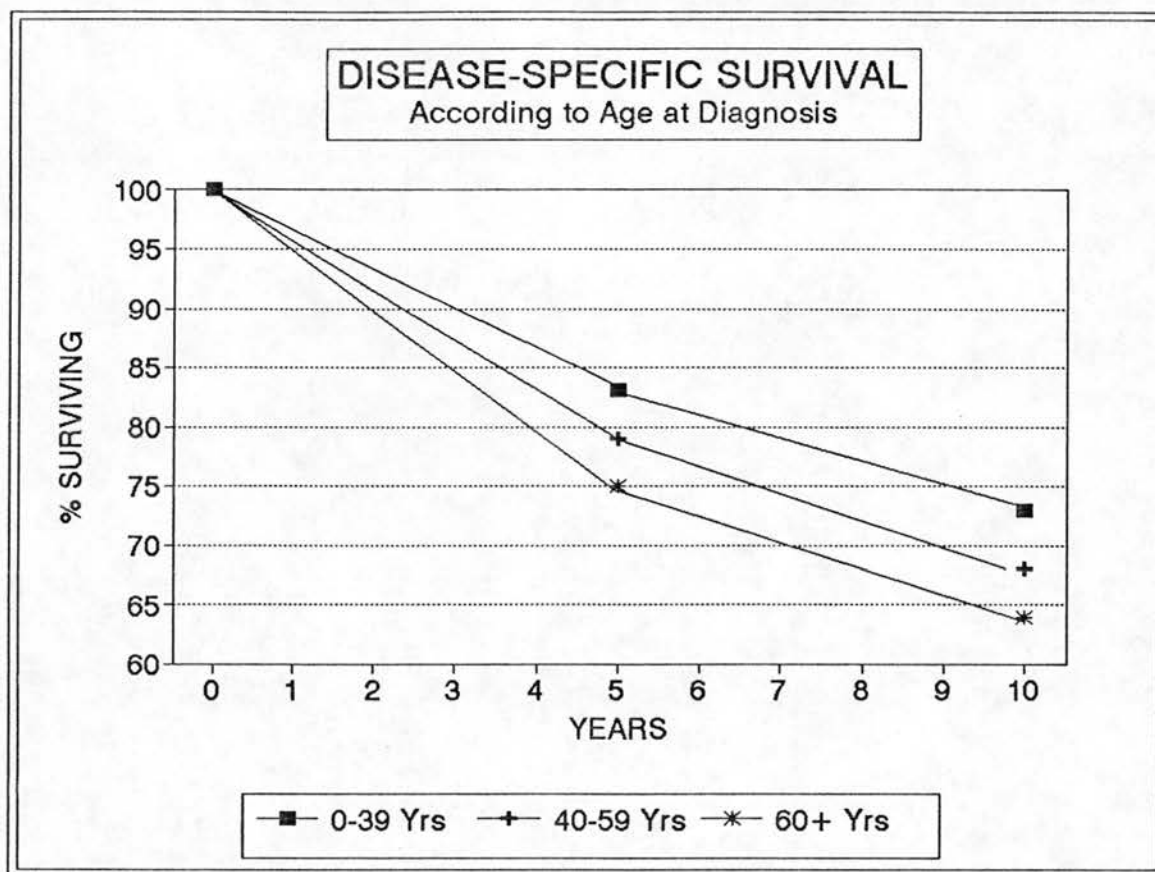
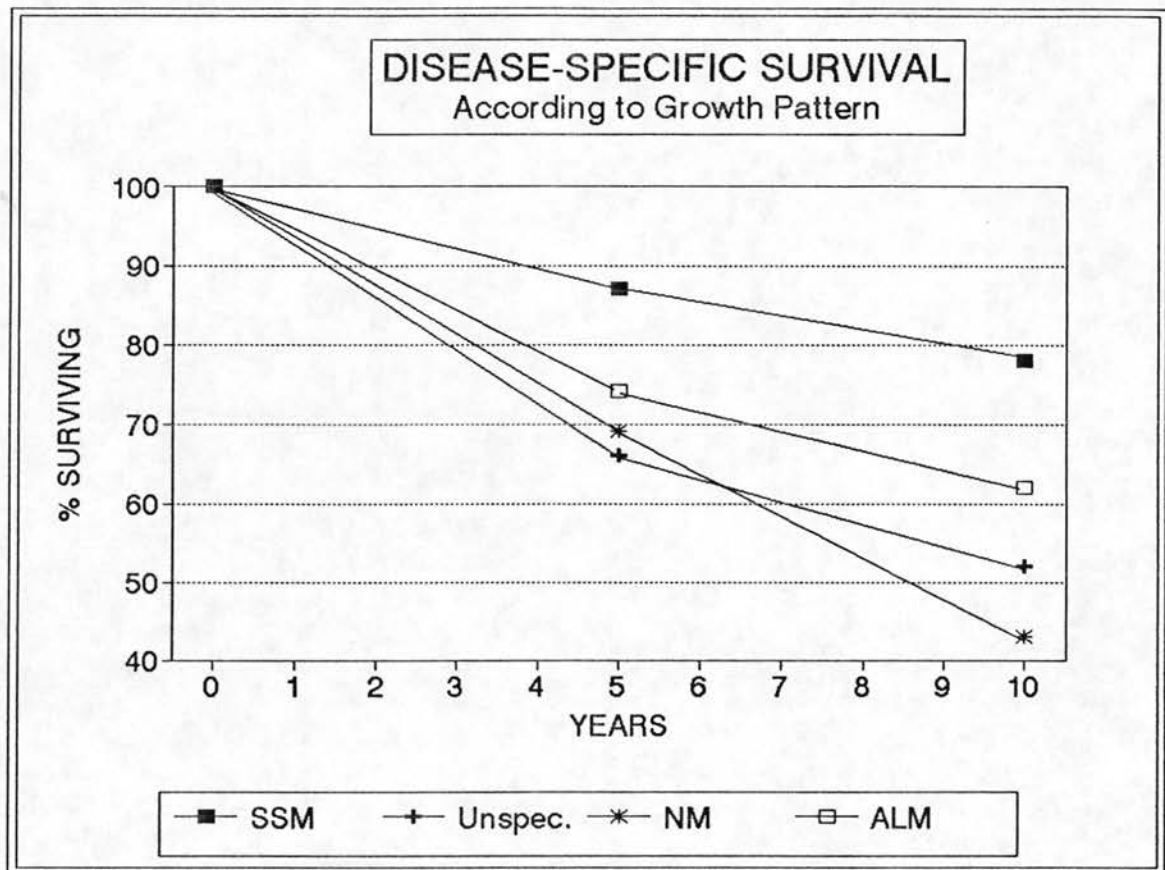


Figure 5



## **4. DISCUSSION**

### **4A. Methodological issues.**

Analysis of survival in patients with stage 1 malignant melanoma is complex, requiring definitions of clinical and histologic features/covariates, follow-up period and statistical methodologies to allow meaningful comparisons of results between centres. The largest single report of prognostic factor analysis in melanoma included a review of world experience up to 1985 [Balch, Soong, Shaw et al., 1985]. Since then, there have been several other significant reports [Johnson, Emrich, Karakousis et al., 1985 : Kopf, Gross, Rogers et al., 1987 : Rogers, Kopf, Rigel et al., 1986 : Worth, Gallagher, Elwood et al., 1989 : Meyskens, Berdeaux, Parks et al., 1988 : Vollmer, 1989 : Karjalainen and Hakulinen, 1988 : Karakousis, Emrich, Rao, 1989 : Drzewiecki, Frydman, Andersen et al., 1990 : Ronan, Han, Das Gupta, 1988].

Lack of uniformity in definition of covariates may lead to difficulties in comparing results of prognostic factor analysis. The desirability of labelling hands and feet as separate primary sites has been suggested [Day, Lew, Mihm et al., 1982]. The extent of lymphocytic infiltration may be defined as 2 or 3 values [Day, Lew, Mihm et al., 1982 : Balch, Soong, Murad et al., 1981 : Van der Esch, Cascinelli, Preda et al., 1981]. The

number of mitoses can be evaluated in random fields or only in areas of most active tumor [Van der Esch, Cascinelli, Preda et al, 1981 : Day, Mihm, Lew et al., 1982], and it can be given the range of values observed or categorised into 2 or 3 groups [Day et al., 1982 : Van der Esch et al., 1981 : Callery, Cochran, Roe et al., 1982]. Inter-observer differences in interpretation of Clark level and Breslow depth are well-known [Prade, Sancho-Garnier, Cesarini et al., 1980]. In a study of consistency among pathologists reporting melanoma, overall agreement was only 70% with one in three disagreeing on each feature [Larsen, Little, Orell et al., 1980]. Growth pattern classification is not always possible and/or reproducible [Larsen, Little, Orell et al., 1980]. Agreement amongst pathologists is least for LMM [70.8%], but greater for SSM and NM. The elective lymph node dissection [ELND] rate and the criteria for the procedure, both of which may influence survival, vary between series. ELND is discussed further in Chapter 4.

The present study had central pathology review in over half the cases but was incomplete by some standards. In the W H O study of prognostic factors in 1159 clinical stage 1 patients, histologic review was absent in 35.5% [Veronesi, 1980]. Even in a large contemporary co-operative review of primary melanoma, the pathology slides were unavailable for review in almost 33% of cases [Western Canada Melanoma

Study ; Worth, Gallagher, Elwood et al., 1989].

The basic distribution of covariates should be assessed when comparing results [Johnson, Emrich, Karakousis et al., 1985]. If a covariate known to be associated with high failure rate were present in one study at a high frequency, it would likely emerge as strongly related to treatment failure, but if present at low frequency, the study may not have sufficient power to detect its significance. The frequencies of clinical and pathological covariates in the present study are discussed in Chapter 2.

End-points of analysis should also be consistent, most importance being attached to disease- specific survival. Some studies have utilised time to visceral recurrence [Day, Lew, Mihm et al., 1982] or metastasis-free survival [Drzewiecki, Frydman, Andersen et al., 1990]. Furthermore, utilisation of different statistical tests to study the same end-point can affect conclusions. Missing data may also affect statistical conclusions. Patient selection in reported series is another factor potentially affecting survival and conclusions about the biological risks of melanoma. Referral centre results are likely to be different from population-based studies. The BCCA, as the only provincial group offering multidisciplinary consultation for melanoma patients and providing most treatments for recurrent melanoma, is likely to have patients with poorer prognosis, with more melanoma



"events" [which may precipitate referral] after diagnosis. Lower survival [5 - year survival of c50%] at referral centres such as Roswell Park Memorial Institute has been attributed to selection bias [Johnson, Emrich, Karakousis et al., 1985].

Guidelines for interpretation of the results of analyses of prognostic factor significance in early breast cancer have recently been reported [Levine, Browman, Gent et al., 1991] and these principles can also be applied to studies of early melanoma. Critical points which should be addressed in reports of prognostic factor analysis include :

1. description of an inception cohort of patients.
2. description of referral pattern.
3. blinded assessment of laboratory and clinical covariates.
4. completeness of follow-up.
5. adjustment for extraneous prognostic factors.
6. appropriate statistical methodology.

#### **4B. Single factor analysis results.**

In the present study, the significant single factors by log rank analysis affecting prognosis were date of diagnosis, sex, primary site including BANS sites, growth pattern, surface description, Clark level,

depth of invasion, clinical and pathological ulceration, tumor diameter and volume, lymphatic invasion, mitotic rate, inflammatory reaction, invasion to stratum corneum, pigmentation, polypoid configuration and type of surgery. Single factor prognostic factor analyses from several recent studies are summarised in Table 6. The original descriptions of prognostic significance of anatomic level of invasion and depth measured by micrometer [Clark, Ainsworth, Bernardino et al., 1969 : Breslow, 1970] are confirmed by all studies which assessed these factors. Other factors which were universally associated with poorer survival were male sex, primary diameter, clinical and pathological ulceration, mitotic rate, poor inflammatory response and lymphatic invasion. Most studies also showed age, primary site, and growth pattern to be significant. Certain factors were insignificant in several studies yet highly significant in others. For example, regression was highly significant [ $p < 0.0001$ ] in the study from Sydney and Alabama, but insignificant in 4 others listed in Table 6. Similarly, surgical treatment [ie elective lymph node dissection] was significant in 2 studies [ $p = 0.0006$  and  $< 0.05$ ], but insignificant in 2 others.

Table 6 over /

**Table 6. Single Prognostic Factor Analyses**

	1	2	3	4	5	6	7
Age	+	+	-	-	+	+	-
Sex	+	+	+	+	+	+	+
Site	+	+	+	+	-	+	+
Diameter	NE	NE	NE	+	NE	+	+
Volume	NE	NE	NE	NE	NE	NE	+
Surface	NE	NE	NE	NE	NE	NE	+
Grth Patt	+	+	-	+	+	+	+
Depth	+	+	+	+	+	+	+
Level	+	+	+	+	+	NE	+
Ulceration							
Clin.	NE	+	NE	NE	NE	NE	+
Path.	+	+	+	+	+	NE	+
Cell type	NE	NE	NE	+	-	NE	-
Inflamm.	+	NE	+	+	+	NE	+
P/I infl.	NE	NE	NE	NE	+	NE	NE
Pigmentn.	+	NE	NE	NE	-	NE	+
Mit rate	NE	NE	-	+	+	+	+
Lymph inv	NE	NE	+	+	+	NE	+
Regression	+	NE	-	-	-	NE	-
Polypoid	NE	NE	NE	NE	+	NE	+
Differrn	NE	NE	NE	NE	+	NE	NE
LND	+	-	+	NE	NE	NE	-
Stage	+	NA	NA	NA	NA	+	NA
BANS	-	-	NE	NE	-	NE	+

Legend for Table 6 :

1 : Balch, Soong, Shaw et al., 1985.

2 : Meyskens, Berdeaux, Parks et al., 1988.

3 : Johnson, Emrich, Karakousis et al., 1985.

4 : Drzewiecki, Frydman, Andersen et al., 1990.

5 : Worth, Gallagher, Elwood et al., 1989.

6 : Ponder, Hunter, White et al., 1981.

7 : Present Study

NE : not evaluated

NA : not applicable

+ = significant

#### **4C. Multivariate analysis results.**

The results of multivariate analysis in the present series showed depth, pathological ulceration, type of surgery and primary site to be significant irrespective of the statistical coding used. In addition, when linear coding was used for categorical covariates, Clark level, growth pattern, BANS sites and lymphatic invasion became significant. Sex was not significant in either model unless adjusted for log depth, suggesting a sex/depth interaction. The frequencies of tumor thickness and primary sites between the sexes are discussed in Chapter 2. Briefly, females had 61%, 55%, 52% and 43% of T1, T2, T3 and T4 primaries. For lower extremity primaries females had 86% of T1 and T2, and for upper extremity primaries had 65% of T1 and T2. In addition, there was an overall dominance of females under 40 years with T1 and T2 primaries.

The inter-relations between female sex, age, primary depth and site have been examined in detail [Shaw, Milton, Farago et al., 1978 : Shaw, McGovern, Milton et al., 1980 : O'Doherty, Prescott, White et al., 1986]. A larger proportion of females had prognostically favorable age [young] and primary sites. Younger females had significantly thinner primaries, but in males and females matched by age, primary site and depth, females with thick tumors still survived longer. Female sex was independently prognostically favorable in 19 of 51 studies [Vollmer, 1989 : Table 7].

In 54 studies utilising multivariate analysis, 42 showed that primary depth is the most frequently significant prognostic factor in malignant melanoma [Vollmer, 1989]. These studies from 18 centres reported on 44-3445 patients [mean 529], mostly stage 1, and used 12 different end-points. Mean and median follow-up times in these studies were 5 and 6 years respectively. Primary depth was also the most significant prognostic factor in the present series and the follow-up time was adequate. Only 5 patients had recurrence beyond 10 years [Chapter 2]. Five other studies of multivariate analysis of survival, not included in the review [Vollmer, 1989], have been identified and are summarised in Table 7. The conclusions in one, however, are limited by the inclusion of only sex, age, stage, year of diagnosis, follow-up year and primary site as covariates : ulceration, depth and other histologic factors were not considered [Karjalainen and Hakulinen, 1988]. All other studies in Table 7 found depth to be consistently related to survival.

Primary depth is associated with several other covariates, particularly ulceration, growth pattern, cell type, mitotic activity, pigmentation, lymphocytic infiltration and primary diameter [Ronan, Han, Das Gupta., 1988] and is largely responsible for the loss of significance of many factors when subject to multifactorial analysis.

#### **4D. Prognostic index.**

Incorporation of primary depth into a prognostic index has been reported to allow accurate prediction of recurrence [Schmoeckel and Braun-Falco, 1978]. The prognostic index is the product of depth and number of mitoses per square millimetre on standard histological sections. The mitotic rate, although significant in single factor analysis in the present study, was not significant in multivariate analysis. In a review of 31 studies of mitotic rate, 14 were positive in multivariate analysis as an independent prognostic factor [Vollmer, 1989]. Of three other reports, one was positive for mitotic rate as an independent prognostic factor [Pondes, Hunter, White et al., 1981 : Worth, Gallagher, Elwood et al., 1989 : Drzewiecki, Frydman, Andersen et al, 1990]. A prognostic index [P I] value of <19 vs >19 has been reported to be an independent prognostic variable for stage 1 melanoma, compared with 7 other predictive variables including depth [Kopf, Gross, Rogers et al., 1987]. For example, patients with melanoma 1.50 - 2.49mm thick had a 5 year survival of 84.1% determined by thickness alone : however, among these patients a sub-group with PI >19 whose survival was only 58% was identified. The present study did not include numeric quantitation of mitotic rate.

#### **4E. Prognostic factors and staging systems.**

The established association of increasing mortality with increasing



depth of primary melanoma forms the basis for the AJCC and UICC staging systems. Unfortunately, the melanoma literature over the past 20 years has not had uniform depth groupings for the purpose of reporting results [Balch, Soong, Shaw, 1985 : Chapter 2]. A method for accurate prediction of survival in both sexes according to depth has been reported [Karakousis, Emrich, Rao, 1989]. In females, 5 year survival was 94% for 1mm thick melanomas and prognosis deteriorated by about 3% for each one millimetre depth thereafter. In males the drop was 9% per millimetre from a 5 year survival of 80% for 1.0mm thick melanomas.

Table 7 over/

**Table 7. Recent Multi-factorial Analyses.**

	1	2	3	4	5	6	7
Age	+	-	-	+	+	-	-
Sex	+	+	+	+	+	-	-
Prim. site	-	+	-	+	+	+	+
BANS sites	-	-	-	-	NE	-	+
Grth pptrn	-	-	-	-	NE	-	+
Depth	+	+	+	+	NE	+	+
Level	-	-	-	-	NE	-	+
Clin ulcer	+	NE	NE	NE	NE	-	-
Path ulcer	-	+	-	NE	NE	+	+
Mit rate	NE	-	-	+	NE	-	-
Epth cells	-	+	-	-	NE	-	-
Lymp invsn	-	-	-	-	NE	-	+
ELND	+	NA	NA	NE	NE	-	-
Wide/ local excsn	NE	NE	NE	NE	NE	+	+

1 : Meyskens, Berdeaux, Parks et al., 1988.

2 : Drzewiecki, Frydman, Andersen et al., 1990.

3 : Worth, Gallagher, Elwood et al., 1989.

4 : Pongdes, Hunter, White et al., 1981.

5 : Karlalainen and Hakulinen, 1988.

6 : Present Study ; binary coding.

7 : " " ; linear coding for categorical covariates.

There is not yet general agreement on the prognostic grouping of primary melanoma according to depth. Analysis of melanoma survival according to primary depth has produced differing results for the appropriate "break-points" between groups. Three reports have reached 3 different conclusions. Reported depth groups are <0.75, 0.76-1.50, 1.51-3.99, >4.00mm [Balch, Murad, Soong et al., 1979] : <0.85, 0.85-1.69, 1.70-3.64, >3.65mm [Day, Lew, Mihm et al., 1981] : <0.85, 0.86-1.95, 1.96-4.00, >4.01mm [Meyskens, Berdeaux, Parks et al., 1988]. For the purpose of stratification in the present U S Intergroup Study of Lymph Node Dissection and Width of Excision in primary melanoma, 3 risk groups are defined, namely <1, 1-4 and >4mm ; the study population is the "intermediate" risk group. The UICC and AJCC staging systems utilise the break-points of Balch, Murad, Soong et al, 1979.

#### **4F. Level and depth of invasion.**

Most studies [40/48] have not shown Clark level to have independent prognostic significance after depth has been considered [Vollmer, 1989]. Only the present study in Table 7 using linear coding for Clark level showed independent significance for that covariate. Variations in coding of Clark level in prognostic factor analysis has been suggested as a contributing factor in the conflicting results of its significance [Vollmer, 1989]. In addition, within each Clark level there is a spectrum of tumor

thickness [Balch, Murad, Soong et al., 1978 : Breslow, Cascinelli, van der Esch et al., 1978 : Chapter 2]. As a prognostic factor, Clark level has been reported to be a better indicator of low risk than depth [Blois, Sagabiel, Abarbanel et al., 1983] : in this review, there was an appreciable death rate for thin tumors at deep Clark levels, and the death rate for level II tumors was minimal [3/226] while there seemed to be no practical minimum thickness which provided comparable predictive accuracy. It remains possible that level of invasion as a biological observation has some advantage over depth as a physical measurement in determining survival in some patients.

#### **4G. Primary site.**

Primary site has been found significant in 25 of 53 multivariate analyses of survival [Vollmer, 1989 : Table 7]. Trunk, head and neck primaries had poorer survival in the present series : BANS sites analysis produced conflicting results according to the statistical coding used. After adjusting for depth, however, BANS sites became significant. Few studies have specifically addressed BANS sites as a potential prognostic factor. Scalp primaries have been reported to have poorer survival than other head and neck sites , even after accounting for sex and depth : as a group, however, BANS sites were not significant [Balch, Soong, Shaw et al., 1985]. Only the present study in Table 7 has shown BANS sites to be

significant. Certain other anatomic sites have been reported to be significant. Volar, subungual, head and neck primaries with subclinical metastases in regional lymph nodes [ie clinical stage 1, pathological stage 3] are almost universally fatal [Day, Mihm, Lew et al., 1982]. Nearly all patients with melanoma of the hands and feet died if the primary was thicker than 2.75mm [Day, Lew, Mihm et al., 1982].

#### **4H. Age.**

Although age is a powerful single prognostic factor, in most multivariate analyses it ceased to be significant [Vollmer, 1989 : Table 7]. Age is associated with depth [Chapter 2 : Balch, Soong, Shaw et al., 1985], the most important prognostic factor. Median primary tumor depth in the third decade was 1.1mm, whereas it was 1.5mm in the fifth decade and 2.8mm in the seventh decade [Balch, Soong, Shaw et al., 1985]. In the University of Arizona experience, young women have the best prognosis, young men and older women have an intermediate prognosis, and older men have the worst prognosis [Meyskens, Berdeaux, Parks et al., 1988]. The Sydney Melanoma Clinic found that survival in women dropped sharply >48 years, approaching that of males [Shaw, McGovern, Milton et al., 1980]. University of California found no difference in survival between females <48 and >48 years, while males <48 years did significantly less well than females of all ages, and significantly better than males >48 years

[Blois, Sagabiel, Arbanel et al., 1982]. Melanoma mortality rates in males and females <50 years in Scotland were not significantly different, but males >50 years had a relatively high risk of death [O'Doherty, Prescott, White et al., 1986].

#### **4I. Primary growth pattern.**

Growth pattern also failed to maintain its significance in most multifactorial analyses. After adjusting for depth or Clark level, growth pattern was insignificant [Table 4]. It was insignificant in all studies in Table 7 and in 35 of 39 studies previously summarised [Vollmer, 1989]. LMM has been found to have a better prognosis, after matching for thickness, than other growth patterns [McGovern, Shaw, Milton et al., 1980]. There were insufficient cases of LMM with complete data in the present series to compare outcomes.

#### **4J. Primary ulceration.**

Primary ulceration is the remaining covariate which has frequently [22/49] been positive in multifactorial analyses [Vollmer, 1989 : Table 7]. Most studies refer to pathologic ulceration. Ulceration width has also been examined. Tumors with ulceration <3mm in width had the same survival as tumors without ulceration [Day, Harrist, Gorstein et al., 1981]. Most ulceration is found in thick tumors [median thickness 3.0mm compared to



1.5mm for non-ulcerated tumors], but studies of ulceration in tumors of equivalent thickness show lower survival in ulcerated tumors [Ronan, Han, Das Gupta, 1988].

#### **4K. Other factors.**

Other less frequently significant prognostic factors in multifactorial analyses include regression [3/29], vascular invasion [4/19], epithelioid cell type [1/5], microscopic satellites [3/14] {Vollmer, 1989 : Table 7}. Degree of cellular differentiation in the primary has been correlated with survival [Allen and Spitz, 1953], but there are difficulties in grading differentiation [Breslow, 1978] which limit its use for prognostic purposes. Poorly pigmented tumors are usually less well differentiated and there are conflicting results of the degree of pigmentation on survival [Ronan, Han, Das Gupta, 1988]. Similarly, for host response/inflammatory infiltrate, there is no uniformity for histology reporting and prognostic factor analyses have produced inconsistent results [Ronan, Han, Das Gupta, 1988]. The loss of power of several of the above factors in multivariate analysis have diminished their value in assessing prognosis.

The conclusion that the type of surgery was significant in multifactorial analysis in the present study differs from most other studies. Specifically, patients undergoing only local excision of the primary did less

well : ELND did not result in better survival than patients not having ELND but the comparability of the two patient groups is debatable [Chapter 4]. Even after adjusting for depth and/or level of invasion, patients having only local excision did less well. Reasons for undertaking only local excision were, however, not assessed during the chart review process. One previous study reported that patients having a biopsy before definitive surgery had a significantly better prognosis [Drzewiecki and Andersen, 1982], but in a further analysis of an expanded data base including the same patients the significance of preliminary biopsy was lost [Drzewiecki, Frydman, Andersen et al., 1990].

The present finding that wide excision is superior to local excision is consistent with current melanoma surgical principles. However, the patient groups [local and wide excision] may not be comparable.

#### **4L. Conclusions.**

In conclusion, the present univariate and multivariate analyses of prognosis in clinical stage 1 malignant melanoma showed that micrometer depth, pathological ulceration, primary site and type of initial surgery were the principal prognostic factors. Alternate models coding primary sites differently showed BANS sites and sex to be significant while primary site ceased to be significant : adjusting this model for Clark level made BANS

sites and sex again significant along with lymphatic invasion. Using linear coding for categorical variables, depth, primary site, pathological ulceration, type of surgery, growth pattern, Clark level, BANS sites and lymphatic invasion were significant [in descending order]. After adjusting for depth, significant factors [in descending order] were Clark level, ulceration, BANS sites, type of surgery, sex and lymphatic invasion.

## **CHAPTER 4**

**ELECTIVE AND THERAPEUTIC**

**LYMPH NODE DISSECTION**

**IN**

**CUTANEOUS MALIGNANT MELANOMA**

## **1. INTRODUCTION.**

- A. Lymphatic spread of melanoma.
- B. Elective lymph node dissection [ELND].
- C. Non-randomised trials of ELND.
- D. Randomised trials of ELND.
- E. Limitations of previous trials of ELND.
- F. Therapeutic lymph node dissection.
- G. British Columbia Cancer Agency experience of lymph node dissection in malignant melanoma.

## **2. PATIENTS AND METHODS.**

- A. Study population.
- B. Statistical methods.

## **3. RESULTS.**

- A. Elective lymph node dissection.
- B. Therapeutic lymph node dissection at primary diagnosis.
- C. Therapeutic lymph node dissection for recurrence.

## **4. DISCUSSION.**



## **1. INTRODUCTION**

### **1A. Lymphatic spread of melanoma.**

Malignant melanoma most frequently spreads via the lymphatic system to the regional lymph nodes [McCarthy, Shaw, Thompson et al., 1988] and may involve any distant organ. Whether the spread of melanoma is always sequential ie. local/regional/distant or whether it may behave like a systemic disease ab initio is debatable. The role of regional lymph nodes in breast cancer has been reconsidered over the past 20 years with the prevailing view that invasive breast cancer is potentially systemic soon after the disease progresses beyond the in situ stage [Henderson, 1987].

The risk of spread of both melanoma and breast cancer is directly related to the accessibility of tumor cells to draining lymphatic and venous channels. Early dissemination by these routes depends upon tumor size and proximity of vessels. In breast cancer, primary tumors are frequently greater than 2 cm diameter whereas the invasive component of primary melanomas fortunately is rarely as deep. Peritumoral lymphatic and vascular invasion in breast cancer [Coppin, Atiba, Worth et al., 1989 : Lee, DeLellis, Silverman et al., 1990] is significantly more frequent than in melanoma, but is associated with a high risk of recurrence if present in the latter [Ronan, Han, Das Gupta, 1988].

Most patients with clinical stage 1 malignant melanoma are cured surgically. For clinical stage 3 patients the prognosis is generally much worse, usually being directly related to the extent of lymph node involvement [Roses, 1985]. For patients experiencing regional lymph node relapse after previous primary melanoma the prognosis is similarly bad [Veronesi, Adamus, Bandiera et al., 1982]. Because surgery is presently the only potentially curative treatment for melanoma and because the risk of lymph node metastasis is known to be related to certain primary characteristics, the concept of earlier surgical intervention in all patients considered at significant risk of lymph node metastasis evolved. This was supported by the observations of superior survival [ $p=0.004$ ] in patients with extremity melanoma with clinical stage 1, pathologic stage 3, compared with clinical and pathologic stage 3 [Roses, Harris, Gumpert et al., 1981]. The origins of elective lymph node dissection are discussed further in Chapter 1.

#### **1B. Elective lymph node dissection.**

Elective lymph node dissection [ELND] is defined as removal of the regional lymph nodes in patients with clinically normal physical examination of these nodes. This procedure is done en bloc with the primary excision where technically feasible observing the same principles as those of Halstead in his operation for breast cancer [Atkins and Hayward, 1967].

However, since the predictability of lymph node involvement in melanoma is considerably short of 100%, the procedure is frequently pathologically negative, making patients and physicians question the therapeutic value of the operation.

ELND protagonists argue that the removal of microscopic or sub-microscopic metastatic disease in regional lymph nodes can prevent the subsequent appearance of distant metastases in some of these patients and that delaying the procedure until the development of clinically positive disease will be associated with an extreme probability of developing distant metastases even if a lymph node dissection is performed at that time [Balch, 1988]. Certainly ELND will not increase the cure rate in patients who do not have metastatic disease in the lymph nodes and this may be up to 60% of patients with primary melanoma. An unnecessary radical operation such as ELND should be avoided if it cannot be shown to be beneficial in reducing recurrence rates and increasing melanoma-specific survival.

#### **1C. Non-randomised trials of ELND.**

Previous reports of ELND in stage 1 malignant melanoma have been of 2 types. Firstly, non-randomised studies of large series of patients have been undertaken by the University of Sydney and the University of

Alabama. The Sidney series excluded patients with head and neck primaries, acral-lentiginous melanoma and lentigo malignant melanoma [McCarthy, Shaw, Milton, 1985]. Survival in men with T3 primaries of the extremities and trunk was 40% better with ELND, and lesser but significant reductions in melanoma mortality were observed in women with T3 and T4 lesions of the extremities. The importance of follow-up for 5-10 years was emphasised since the survival curves separated most strikingly during this time. The Alabama series [Balch, Soong, Milton et al., 1982] reported better survival at 10 years of follow-up in all patients with trunk and extremity T1-3 primaries, and this was most marked in males with T2 lesions. ELND has also been reported to have survival benefit in intermediate thickness [0.76-4.0 mm] melanoma of the trunk and extremities in a study from North Carolina [Reintgen, Cox, McCarty et al., 1983]. This non-randomised study was analysed according to whether or not patients had ELND compared with a concurrent control group, and also by multifactorial analysis with other possible factors predictive of survival. Death rate from melanoma was reduced from 12% to 5% in patients having ELND [ $p=0.05$ ] and by multivariate analysis the significant factors were ulceration of the primary [ $p=0.0008$ ], thickness [ $p=0.008$ ] and ELND [ $p=0.01$ ]. A smaller study of intermediate thickness melanoma [1.51-3.99mm], however, failed to show a survival benefit from ELND [Elder, Guerry, Van Horn et al., 1985]. This study was analysed comparing

survival curves, and prognostic factors were assessed by multi-factorial analysis. Favorable prognosis was associated with low mitotic rate, age between 40-59 years and lymphocyte response around the primary.

A retrospective review of 272 patients with melanoma of the trunk, of whom 184 underwent ELND, reported 10 year survivals of 85 and 38% for ELND negative and positive patients [Ariel, 1982]. In this series, 62 patients had no ELND : in these patients, 10 year survival was 67% for those who had no relapse in regional nodes and 23% for those who had.

#### **1D. Randomised trials of ELND.**

Two prospective randomised trials have been undertaken, one by the World Health Organisation Melanoma Group [Veronesi, Adamus, Bandiera et al., 1977] and another by The Mayo Clinic [Sim, Taylor, Pritchard et al., 1986]. The WHO Trial randomised 522 stage 1 and 31 stage 2 patients with extremity melanoma to wide excision with immediate ELND or "delayed LND". Females predominated [81.4%] and lower limb was the commonest primary site [82.8%]. Survival curves of the 2 treatment groups were superimposable and no subset of patients had significant survival benefit from ELND.

The Mayo Clinic study had 3 treatment options drawn at random,

namely no ELND, immediate ELND and "delayed ELND" [performed 2-3 months following primary surgery]. Of the 171 patients in the study, 103 had primary depth less than 1.5mm. Head and neck melanomas were not included. There was no difference in survival between the 3 treatment groups at median follow-up time of 4.5 years. Of 36 "melanoma events" in the control group, 12 were regional lymph node metastasis and 11 were distant metastasis ; 14 patients had therapeutic lymph node dissection for recurrence [RTLND].

#### **1E. Limitations of previous trials of ELND.**

Both the randomised and non-randomised studies discussed above have limitations [Balch, 1988]. These most cited are ;

- a) the large number of females with lower extremity lesions [with an inherently better prognosis and hence a lesser likelihood of showing a survival benefit with ELND] in the WHO Trial.
- b) more patients with ulcerated primaries in the ELND arm of the WHO Trial.
- c) 66% of patients in the Mayo Clinic Trial with T1 or T2 primaries.
- d) the exclusion of head and neck melanomas from both randomised trials and the Sydney series.
- e) problems of identification of an appropriate control group with whom to compare results in the non-randomised studies.



## **1F. Therapeutic lymph node dissection.**

Therapeutic lymph node dissection [TLND] is generally accepted as the treatment of choice for patients with clinically positive lymph nodes in the absence of evidence of systemic spread of melanoma ie clinical stage 3 at diagnosis [Balch, Urist, Maddox et al., 1985]. TLND is also recommended for patients with regional lymph node recurrence [Recurrence {R} TLND] from previous melanoma.

## **1G. British Columbia Cancer Agency Experience of Lymph Node Dissection in Malignant Melanoma.**

The Melanoma Tumor Group of the British Columbia Cancer Agency [BCCA] recommended in 1976 that ELND be undertaken in "high risk" clinical stage 1 malignant melanoma defined as primary tumor of Clark level 3 and >0.76mm depth of dermal invasion, Clark level 4 or 5, and in whom one anatomic lymph node drainage site could be identified. This recommendation was modified in 1983 to stage 1 patients with tumors >1.5mm depth.

This study reports the BCCA experience of ELND and TLND [at diagnosis and at recurrence] in malignant melanoma with a minimum follow-up of 7.9 years. Factors influencing the ELND positivity rate are presented. Survival in ELND patients is compared with other reported

series of randomised and non-randomised patients and is compared with a concurrent control group of clinical stage 1 patients treated in the same decade without ELND [designated hereafter BCCA Control patients]. Reasons for omitting ELND included patient and referring surgeons' decisions in the light of possible expected benefits.

The effect of ELND on survival of all patients with clinical stage 1 malignant melanoma registered at BCCA during the study period has been analysed by multifactorial analysis according to whether or not they underwent ELND. Survival after TLND and RTLND has been analysed and compared with other reported series.

## **2. PATIENTS AND METHODS**

### **2A. Study population.**

In 1983 a retrospective review of all patients registered in the BCCA with malignant melanoma from June 1 1972 to May 31 1981 was commenced. Full details of the patient population and reasons for exclusion are described in Chapter 2. In summary, 1944 patients were registered with malignant melanoma in the Provincial Cancer Registry, 1245 of whom were referred to the BCCA. Final analysis was undertaken on 891 patients. Reasons for exclusion are described in Chapter 2. All patients who underwent ELND, TLND and RTLND were included. TLND

was defined as lymph node dissection in patients with clinically positive or equivocal regional lymph nodes. Lymph node dissection surgery with curative intent was performed by referring surgeons throughout the province usually after consultation with members of the Melanoma Tumor Group. Surgical morbidity was not assessed retrospectively. Data on 147 demographic, histopathologic, treatment and outcome variables were extracted from the medical records of the study population, computerised and analysed according to the methods in Chapter 2. The data base was updated in April 1990 to provide minimum follow-up of 7.9 years. Survival times were calculated from date of diagnosis to date of death, last written or physician contact.

Clinical stage 1 patients who did not have an elective lymph node dissection for various reasons during the study period were identified [BCCA Control patients]. Full clinical and pathological factor profiles were obtained and follow-up recorded to permit comparison with the concurrent ELND patients.

## **2B. Statistical methods.**

Analysis of data was undertaken with the Statistical Package for Social Science [SPSS-X release 3.1]. Survival curves were generated using the product limit method [Kaplan and Meier, 1958] with a biomedical

computer program BMDP [Dixon, 1981]. Cases with missing data were excluded from the relevant analysis procedure. Multifactorial analysis was undertaken using the proportional hazards model [Cox, 1972]. Differences between survival curves were calculated using the log rank test [Peto, Pike, Armitage et al., 1977].

### **3. RESULTS**

#### **3A. Elective Lymph Node Dissection.**

Elective lymph node dissection was performed in 232 patients, 111 male and 121 female. In 9 cases, clinical evaluation of the regional lymph nodes was unspecified and accounts for discrepancies in totals in Tables 1 and 2.

In patients with specified negative clinical evaluation of regional nodes, ELND was pathologically positive in 20 [19%] males and 16 [14%] females, for a combined positivity rate of 16%. ELND positive/negative frequencies and overall % positivity according to primary site, primary growth pattern, depth of invasion and Clark level are summarised in Table 1.

Depth measurements were available in 208 patients undergoing ELND. Ranges and median depths of primary tumors in patients with

positive and negative ELND were 0.85-8.0mm and 3.0mm, and 0.45-7.00mm and 1.6mm respectively. Median depth of primary tumors in all ELND patients was 1.70mm, and 1.00mm in 530 BCCA Control patients [ $p<0.0001$ ].

In patients with positive ELND, 18 had 1 node positive, 7 had 2 nodes positive and 8 had 3+ nodes positive ; 3 patients had an unspecified number of nodes positive. Three patients with positive ELND had 1-5 nodes examined, 9 had 6-10, 6 had 11-15 and 11 had 16 + nodes examined ; 7 patients had an unspecified number of nodes examined. Of the ELND negative patients, 5 had 1-5 nodes examined, 4 had 6-10, 4 had 11-15, 14 had 15 + nodes examined ; 120 patients had an unspecified number of nodes examined.

Disease recurred in 47 [25%] of ELND negative patients with median survival 9.09 years from time of diagnosis for all ELND negative patients. There were 23 [64%] recurrences in ELND positive patients with median survival 4.16 years and 37% 10 year survival.

Levels of primary invasion and depth in stage 1 ELND patients and BCCA Control patients are presented in Figures 1 and 2. Level IV primaries dominated the ELND series [61% of all cases]. Primary depth

was unspecified in 25% of BCCA Control patients and 4% of ELND patients. In patients with depth measurements, more ELND patients had T2-T4 primaries and, as noted above, the median depth of primaries of ELND patients was significantly greater. Females accounted for 53% of the ELND patients and 54% of the BCCA Control patients. Primary site distribution in ELND and Control patients is shown in Figure 3.

Ten year disease-specific survivals according to level of invasion and depth in BCCA ELND and Control patients are shown in Figures 4 and 5. Survival differences were significant in favor of ELND patients when grouped according to either level of invasion or depth [ $p < 0.0001$ ]. The group [T2 primary] with the largest difference in survival [23%] had only 5 pathologically positive lymph node dissections [7%] out of a total of 73.

Univariate and multivariate analysis of survival was undertaken in 720 clinical stage 1 patients of whom 192 had local excision [L.E.], 3 had L.E. + ELND, 327 had wide excision [W.E.], and 198 had W.E. + ELND [Chapter 3]. Ten year disease-specific survivals for patients undergoing different surgical procedures were 38% for L.E., 50% for L.E. + ELND, 67% for W.E., and 67% for W.E. + ELND [Figure 6]. Multivariate analysis did not show ELND to be a significant factor determining prognosis. By univariate analysis, patients having only local excision had significantly poorer

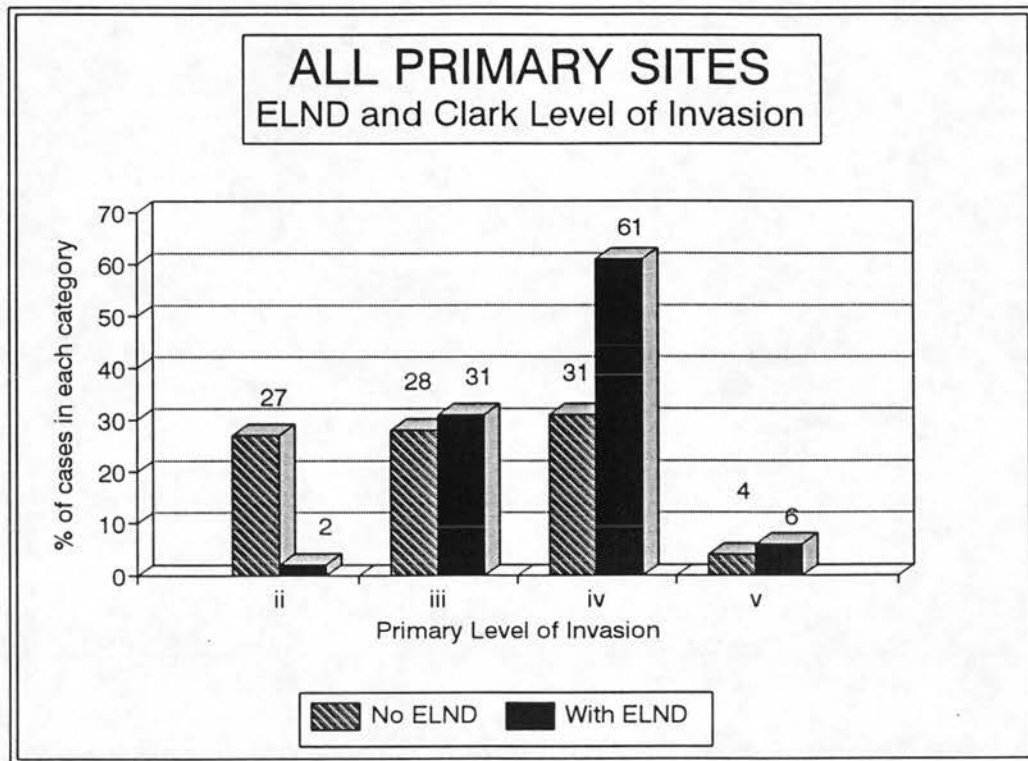


survival [p=0.0472], and this was still significant in multivariate analysis [p=0.0015].

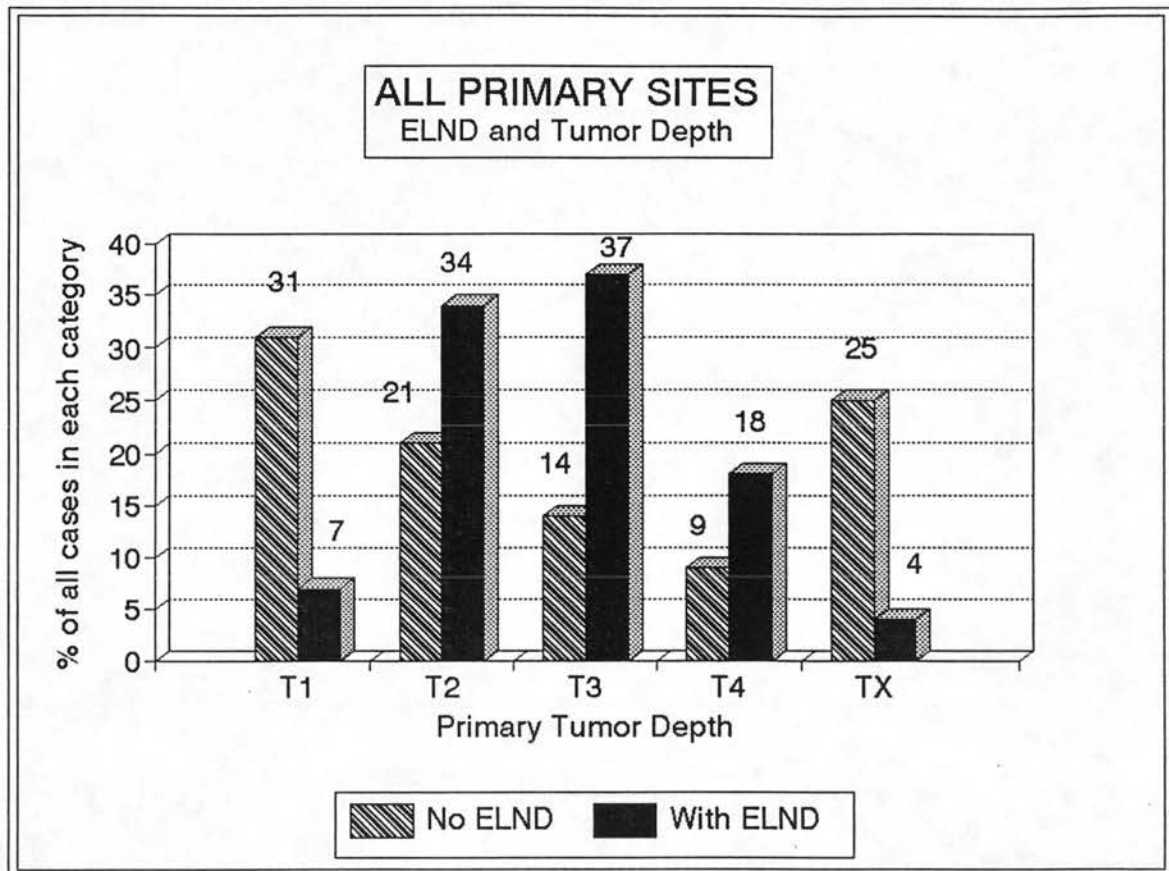
**Table 1. Patient Characteristics.**

		<b>ELND +ve</b>	<b>ELND -ve</b>
Sex	Males	20	86
	Females	16	102
Primary Site	Upper Limb	3	42
	Lower Limb	16	76
	Head & Neck	5	24
	Trunk	12	45
Growth Pattern	SSM	16	103
	NM	15	57
	LMM	0	1
	NOS	5	23
Primary Depth	T1	0	15
	T2	5	68
	T3	12	66
	T4	14	20
	Unspecified	5	4
Clark Level	1	0	1
	2	0	4
	3	3	64
	4	25	106
	5	6	8

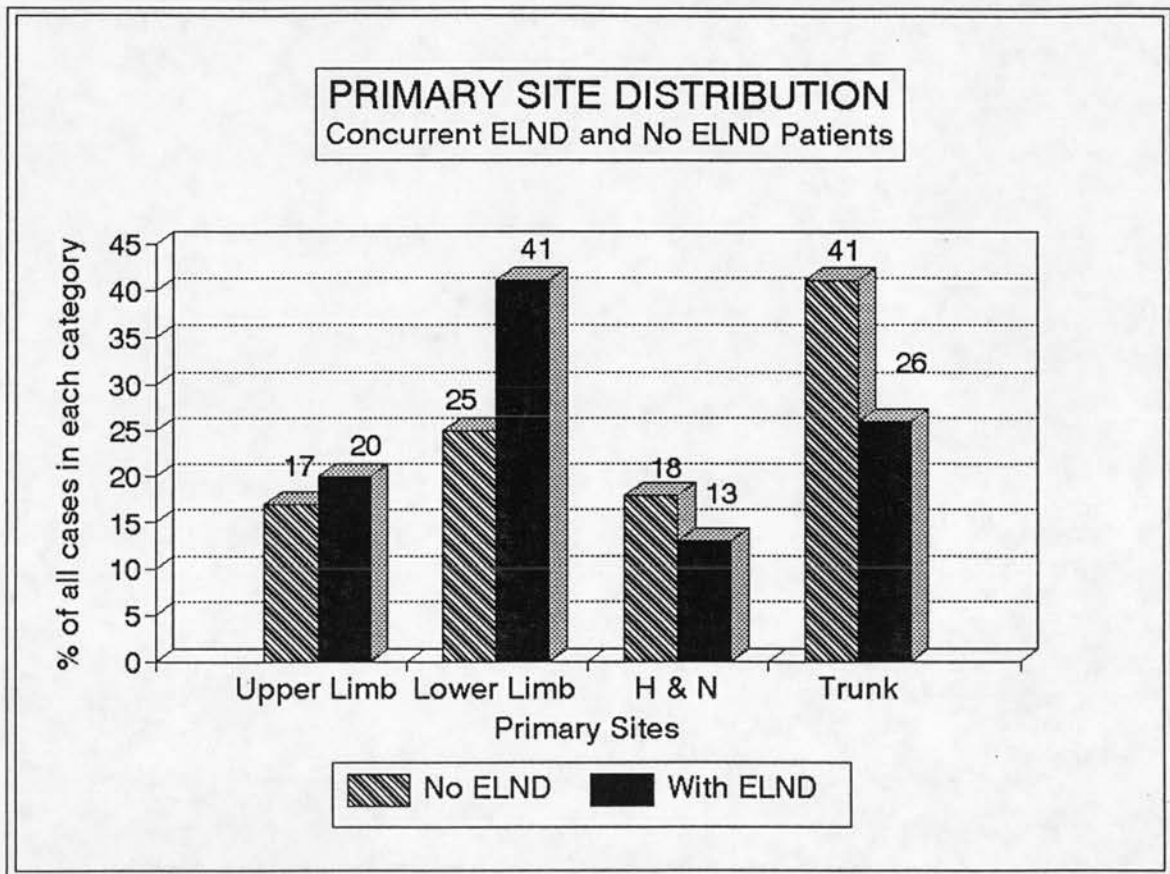
**Figure 1**



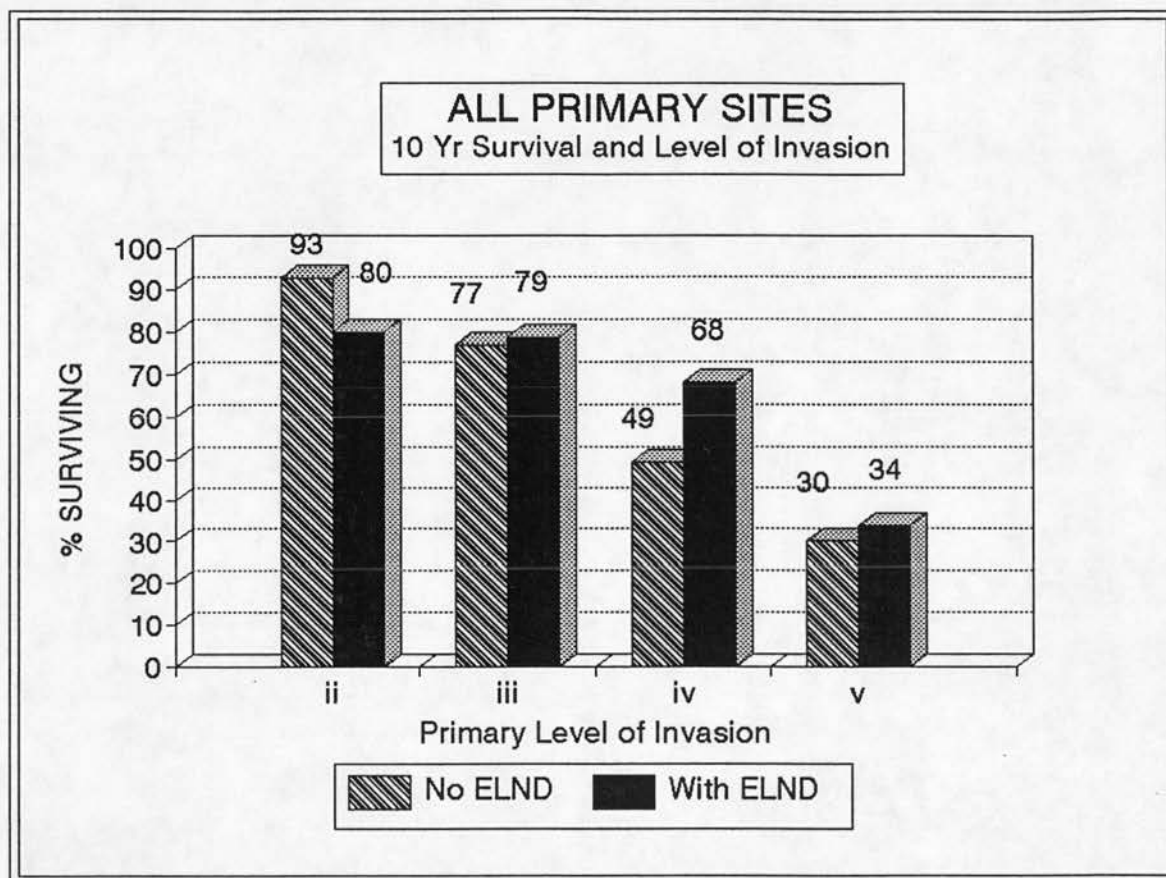
**Figure 2**



**Figure 3**



**Figure 4**



**Figure 5**

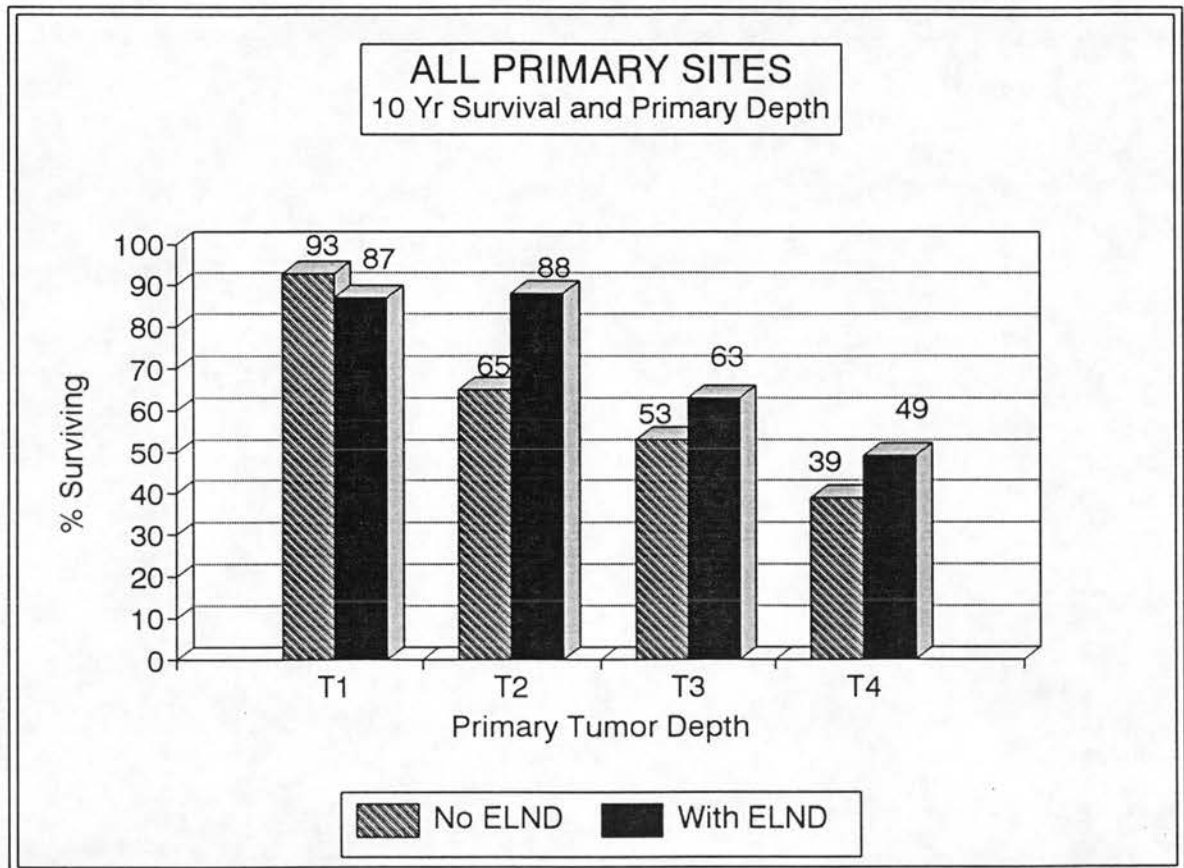
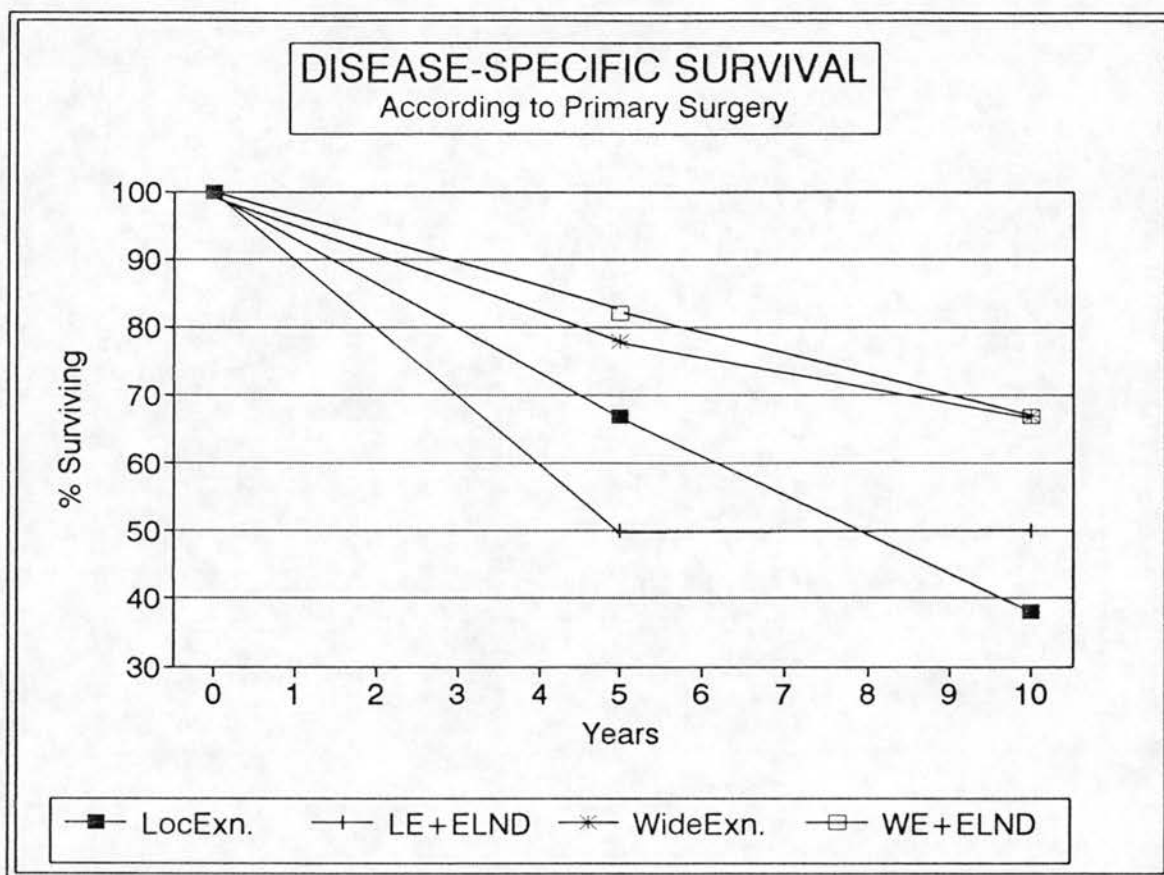




Figure 6



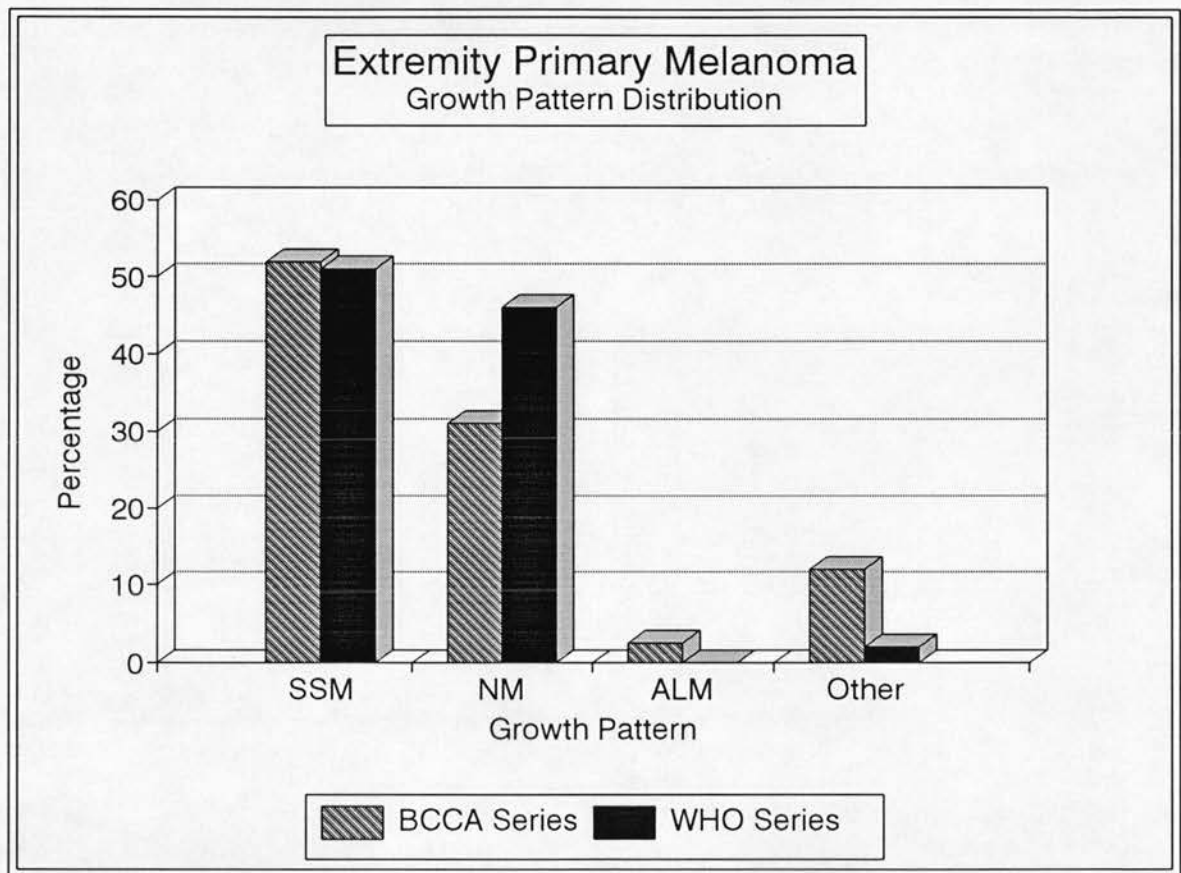
Survival analysis was undertaken in the subset of patients with extremity primary melanoma undergoing ELND to permit outcome comparison with patients in the WHO series [Veronesi, Adamus, Bandiera et al., 1982]. Growth pattern and depth distributions for both series are shown in Figures 7 and 8. The WHO series had more patients with melanomas >3.5mm thick and fewer patients with melanomas <3.5mm thick. Respective 10 year survival percentages in the present series and the WHO series were 80 and 62%. Further survival comparisons for patients in both series with superficial spreading melanoma [SSM], nodular melanoma [NM], Clark level III and IV, and melanomas less than 3.5mm thick are presented in Figure 9. All the BCCA survivals are in the range 11-25% better. Survival in the WHO series was calculated actuarially but this is unlikely to explain the survival differences between the 2 series [Veronesi, Adamus, Bandiera et al., 1977 : Veronesi, Adamus, Bandiera et al., 1982]. Median primary tumor depth was not reported in the WHO series but was probably greater than in the BCCA series and could account for the survival differences.

Three further sub-groups of patients were identified in the present series to allow comparison of outcome in patients who appeared to benefit most from ELND in the University of Sydney series ie males with T3 trunk primaries, males and females with T3 extremity primaries [McCarthy,

Shaw, Milton, 1985]. Acral-lentiginous melanomas were excluded. Ten year survivals for 4 groups of patients are shown in Figure 7 : ELND patients in Sydney and BCCA, and non-ELND Sydney and BCCA patients. Patient numbers for each of these groups were 81, 19, 104 and 26 [T3, male, trunk], 55, 11, 61 and 4 [T3, male, extremity], 71, 41, 135 and 18 [T3, female, extremity]. Survival differences between the 2 cohorts of BCCA patients, ELND and Control, for these specific sex and primary site groups were not significant [ $p=0.1175$ ]. The numbers of patients in the BCCA ELND groups were, however, small, especially T3 male extremity primary patients. Survivals for all BCCA patients in these categories were intermediate between those of Sydney non-ELND and ELND patients.

Figure 7 over/

**Figure 7**



**Figure 8**

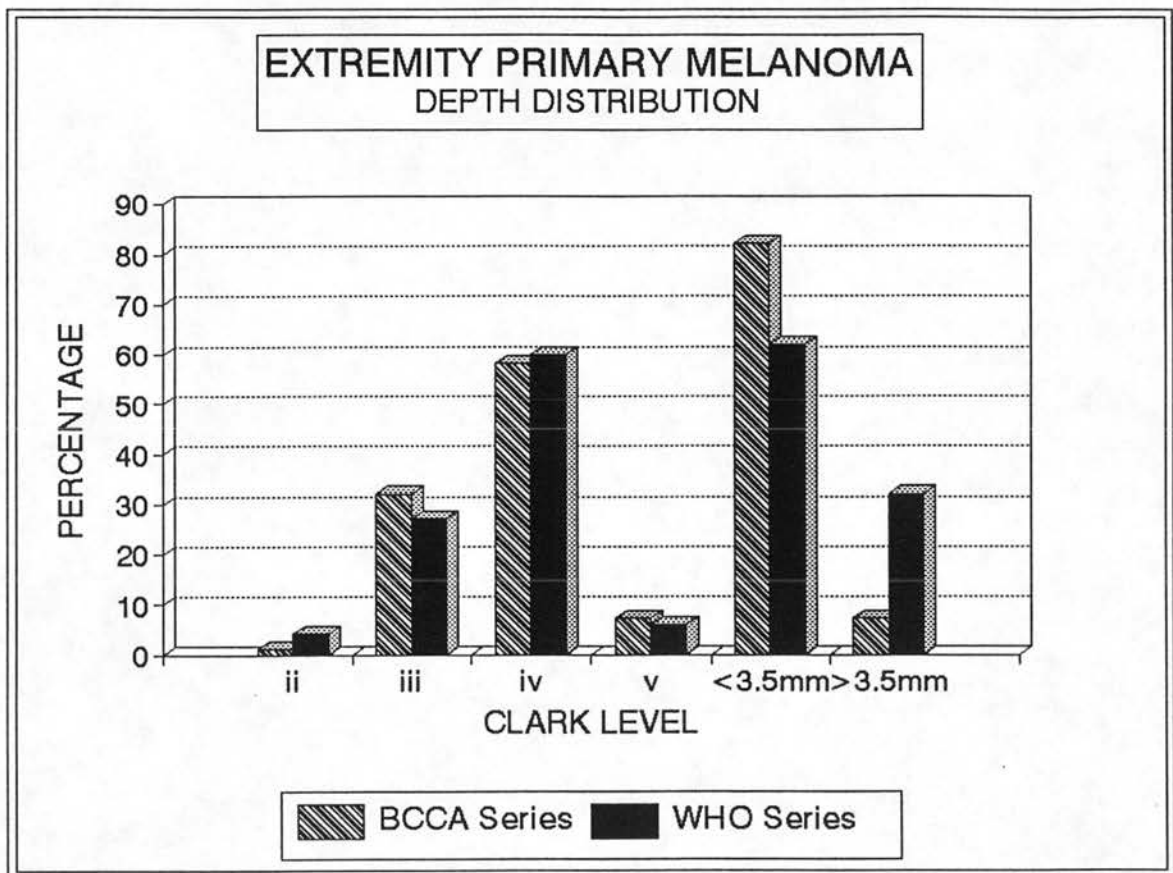
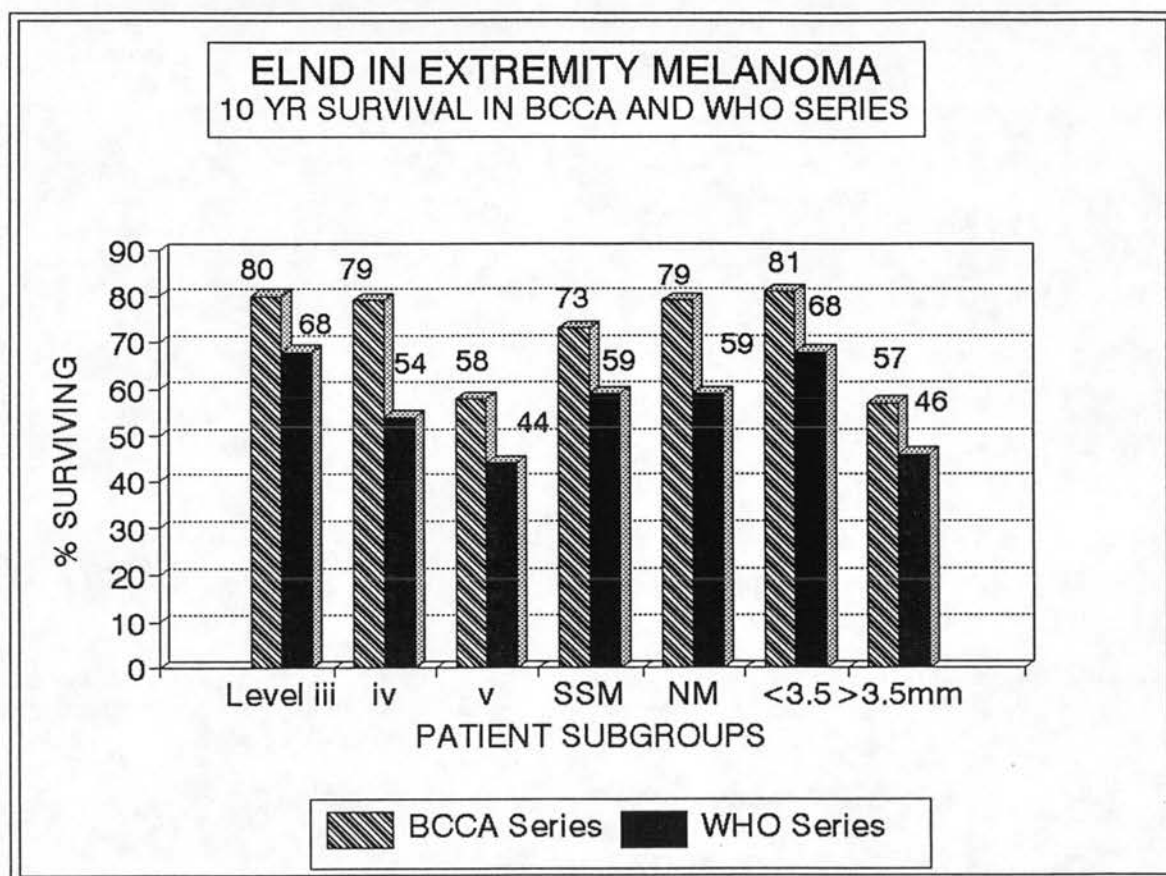


Figure 9





### **3B. Therapeutic Lymph Node Dissection [TLND] at Primary Diagnosis.**

Therapeutic lymph node dissection was performed in 50 patients at primary diagnosis and 36 [72%] were positive pathologically. TLND was positive in 24 [66%] males and 12 [33%] females. Of TLND positive patients, 12 had 1 node positive, 3 had 2 positive, 12 had 3 + nodes positive and 9 had an unspecified number of nodes positive.

Primary tumor depth measurements were available in 24 patients with positive TLND. Range and median depth of primaries were 1.67-8.0mm and 2.0mm respectively. Disease recurred in 24 [67%] positive TLND patients and median survival was 2.7 years.

### **3C. Therapeutic Lymph Node Dissection for Recurrence [RTLND].**

Of the entire series of 891 patients, 537 had clinical stage 1 disease without having ELND, and 125 of them developed regional lymph node recurrence. TLND for recurrence [RTLND] was performed in 90 of these patients. Range and median depth of responsible primaries in RTLND patients were 1.0-7.0mm and 2.0mm respectively. Median time to regional lymph node recurrence from primary treatment was 1.5 years. For all patients who underwent RTLND, median survival was 1.8 years from the date of recurrence and 4.4 years from date of primary diagnosis : 10 year survival was 26%. Analysis of extent of lymph node positivity was not

undertaken in these patients.

Survival comparisons were made between all 3 groups of BCCA lymph node dissection positive patients ie ELND +ve, TLND +ve and RTLND. Survival was defined from the date of LND positive surgery. No statistically significant difference in survival was demonstrated [Figure 11].

Figures 10 and 11 over /

**Figure 10**

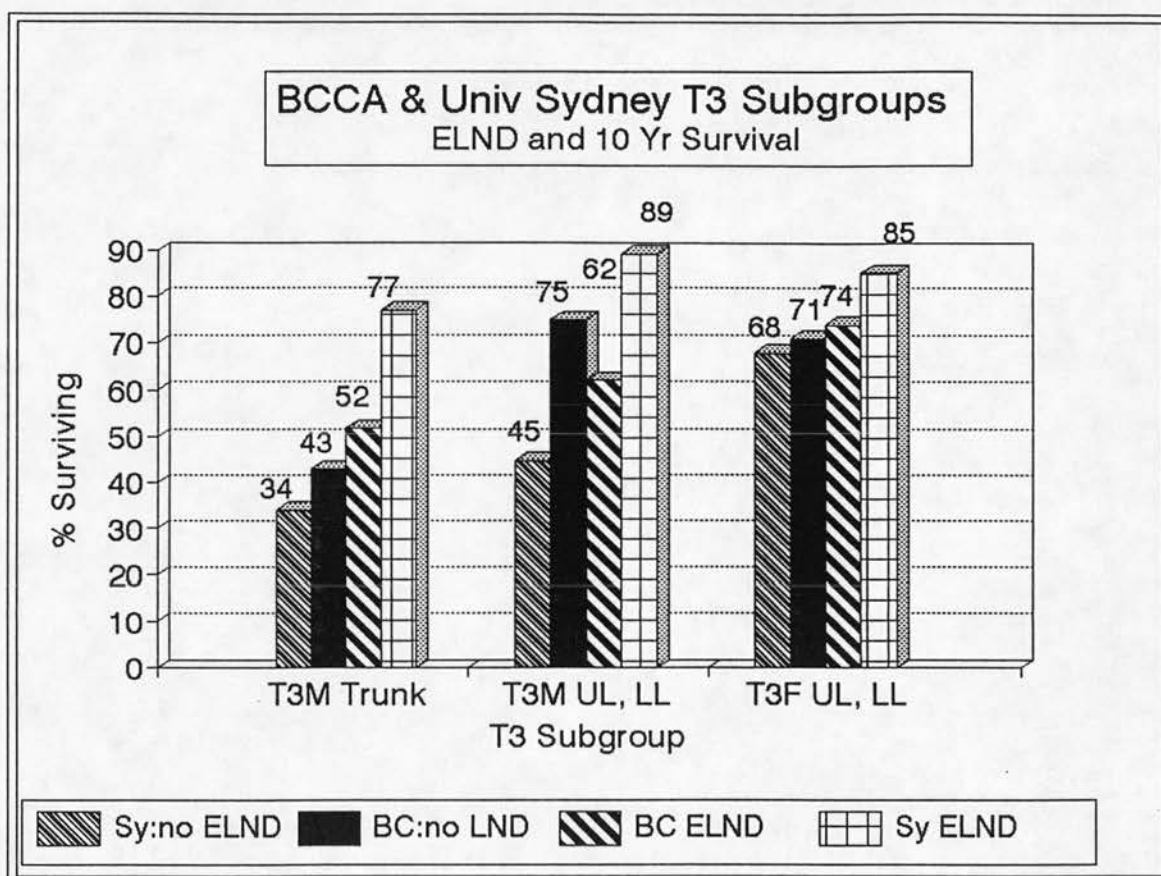
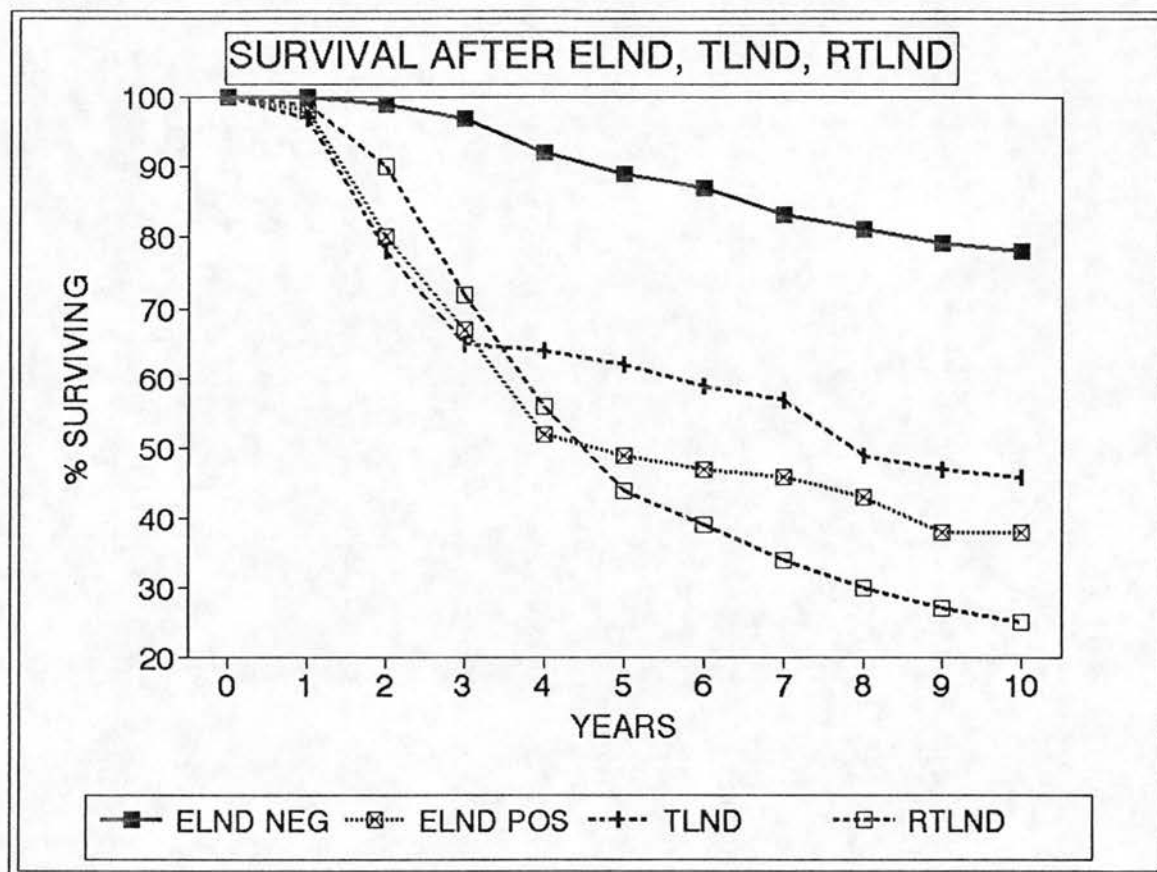


Figure 11



#### 4. DISCUSSION

The role of elective lymph node dissection [ELND] in surgical management of cutaneous melanoma has been extensively studied in both non-randomised [McCarthy, Shaw, Milton, 1985; Balch, Cascinelli, Milton, 1982; Reintgen, Cox, McCarty et al., 1983] and randomised [Veronesi, Adamus, Bandiera et al., 1982; Sim, Taylor, Pritchard et al., 1986] clinical trials. Results of randomised trials have not confirmed the results of the non-randomised studies, although re-analysis of the World Health Organisation Trial suggested that a subgroup of patients with intermediate risk of recurrence did have a superior survival with ELND [Balch, Cascinelli, Milton et al., 1985].

The results of ELND in melanoma have previously been reported in terms of :

- A. "yield" i.e. % probability of detecting lymph node metastases.
- B. disease-free and overall survival.
- C. its contribution as a prognostic factor in multifactorial analysis of survival.

The importance of follow-up from 5-10 years has been emphasised because of the observation that survival differences between patients receiving wide excision + or - ELND do not become apparent until then

[McCarthy, Shaw, Milton, 1985]. Follow-up in the present study was 7.9 - 16.9 years and is therefore adequate to draw comparisons with other series.

The yield of microscopically positive lymph nodes from ELND in this study [16%] is within the range [4-25%] of previous reports [McCarthy, Shaw, Milton, 1985; Veronesi, Adamus, Bandiera et al., 1982]. Yields according to primary tumor depth are also consistent with previous reports of 5-10% for T2 , 17-20% for T3 and 39% for T4 tumors [Holmes, Mosely, Morton et al., 1977; Wanebo, Woodruff, Fortner, 1975]. Interestingly, the series with the lowest reported overall yield [4%] showed the largest treatment effect of ELND, suggesting that patients with a "negative" ELND may in fact be those who are likely to benefit most from the procedure. The difference between the yield [16%] in this study and the eventual lymph node relapse rate of 23% in patients with clinical stage 1 disease not undergoing ELND suggests that there are still patients with lymph node metastases which may not be identified at ELND. A regional lymph node relapse rate of 57% in patients with melanomas 1.5mm+ in thickness treated by wide excision alone [Balch, Murad, Soong et al., 1979] is greater than the expected yield of ELND and supports this conclusion. Similarly, in the WHO Trial, 21% of patients with melanomas 1.5-4.9mm thick were ELND positive but the RTLND rate in the control group was 56%.



The extent of lymph node positivity in ELND positive patients [all primary sites] in the present series is similar to the WHO experience in extremity melanoma [Veronesi, Adamus, Bandiera et al., 1982]. Proportions of patients with 1, 2, 3+ and unspecified positive nodes were 50% and 46%, 19% and 22%, 22% and 20%, 8% and 11% between the present series and the WHO series respectively.

The yield of microscopically positive lymph nodes from ELND according to primary growth pattern has been compared with a previous report which attempted to correlate histologic features of the primary with the likelihood of occult regional lymph node metastases [Harrist, Rigel, Day et al., 1984]. The percentage positivities for SSM and NM were almost identical [13 and 11% for SSM, and 21 and 23% for NM]. Multivariate analysis showed that primary depth, presence of microscopic satellites, and the time interval between diagnosis and ELND were most highly associated with occult regional node metastases [Harrist, Rigel, Day et al., 1984].

The Australian series excluded patients with head and neck primaries, acral-lentiginous [ALM] and lentigo malignant melanoma [LMM] patients [McCarthy, Shaw, Milton, 1985]. Excluding head and neck primary patients in the present series reduces the yield to 15% and ALM and LMM accounted for only 4 patients. The present series had more T2 [34%

compared to 27%] and fewer T1 [7% compared to 15%] and this may partly explain the difference in yield between the series.

In addition to the false negative rate in clinical assessment of regional nodes, the problem of false positivity arises in patients with palpable nodes. In the present series, 28% of patients with palpable nodes were negative on pathological examination. A similar false positive rate [27%] has been previously reported [Karakousis, Seddiq, Moore, 1980].

Survival of BCCA ELND patients has been compared with 3 different series of patients :

1. BCCA Control clinical stage 1 patients concurrently treated without ELND.
2. WHO series of extremity primary melanoma patients.
3. University of Sydney patients with melanoma of the trunk and extremities.

Although the depth of invasion among BCCA ELND patients was significantly greater than in concurrent BCCA Control patients, 10 year survivals were significantly better, especially for T2 and level IV primaries. However, Clark Level IV primaries accounted for 43% of T2, 73% of T3 and 65% of T4 primaries ; conversely, T2 primaries accounted for only

29% of Level IV primaries, and T3 and T4 primaries accounted for 65% [Chapter 2]. These figures suggest that other factors besides ELND are involved in the survival differences. BCCA ELND patients had more favorable primary sites, more lower limb and fewer trunk, head and neck primaries. Primary site was an independent prognostic factor for survival [Chapter 3]. In addition, ELND was only performed when a single lymphatic drainage area was present ; patients with midline or watershed primaries did not have ELND. Multifactorial analysis of prognostic factors did not show ELND to be significant [Chapter 3].

The results of survival analysis in BCCA extremity primary melanoma patients undergoing ELND have been compared with those from ELND patients in the WHO Trial [Veronesi, Adamus, Bandiera et al., 1982]. In all levels of invasion, depth groups and growth patterns examined, BCCA patients had apparently better survival, likely related to other prognostic factor differences between the 2 groups of patients. Depth of invasion was greater in the WHO patients [36% primaries >3.5mm thick compared with 11% in the BCCA series : 45% T4 primaries compared with 25% T4 primaries for all sites in the BCCA series].

The subgroups of patients reported to benefit most from ELND in the University of Sydney experience were males with T3 primary melanomas

of the trunk and extremities, and females with T3 extremity melanomas [McCarthy, Shaw, Milton, 1985]. BCCA ELND patients in these subgroups did not have a significant survival advantage over patients in the same subgroups from the BCCA Control group. Survival in BCCA ELND patients in these subgroups was inferior to the Sydney ELND patients and survival in the BCCA Control subgroups was superior to the Sydney non-ELND patients. Overall, the results in BCCA patients would not support the proceeding with a prospective randomised trial for T3 melanoma of the trunk and extremities.

Median survivals for ELND and TLND positive patients were 3.3 and 1.7 years respectively in a series from University of Illinois [Das Gupta, 1988]. Median survivals for ELND positive patients were reported in terms of number of nodes positive [1 node : 4.8 years ; 2,3 nodes : 5.4 years ; 4+ nodes : 4 years ;  $p = \text{NS}$ ] in a series from New York and median survival for TLND positive patients was 2 years [Roses, Provet, Harris et al., 1985]. For extremity primary melanoma patients having ELND, median survival for ELND negative patients was in excess of 25 years, and 4.3 years for ELND positive patients [Roses, Harris, Ackerman, 1983]. Median survivals for ELND positive patients [2 years] and combined TLND and RTLND patients [2.2 years] have been reported from Roswell Park [Karakousis, Seddiq, Moore, 1980].

Median survival of ELND positive patients in the present series [4.2 years] was superior to the University of Illinois and Roswell Park series and consistent with the WHO and New York series. Median survival of ELND negative patients [9.1 years] is comparable to a previous report of 8.1 years [Karakousis, Seddiq, Moore, 1980]. Survival for TLND positive patients in the present series [2.7 years] appears superior to the Illinois, Roswell Park and New York series.

Survival in ELND positive patients has been analysed to identify subgroups with better survival [Koh, Sober, Day et al., 1986]. A group with primary tumor depth <3.5mm and <20% of lymph nodes positive had a 7-year survivorship of 66%. Within that subgroup, patients with primaries on the trunk or extremities [excluding hands and feet] had a 7-year survivorship of 76%. The group with tumors >3.5mm thick primaries and >20% positive nodes had a 7 year survival of 29%. It was recommended that this finding be considered in stratification in adjuvant trials of ELND positive patients.

There are two current prospective randomised trials addressing the role of elective lymph node dissection. An American Inter-Group Study includes patients with intermediate thickness [1-4mm] clinical stage 1 melanoma of the trunk and extremities with randomisation to immediate

ELND or not, and either a 2 or 4 cm diameter excision margin around the primary. The accrual goal is 1500 patients. The WHO Melanoma Group is studying trunk primary melanoma, clinical stage 1 and >2mm thick. Randomisation is between wide excision +/- ELND. Therapeutic node dissection would be offered to patients in the non-ELND group who develop resectable regional node metastases. It is hoped that the benefits, if any, will be shown by these trials. Results are not expected to be available for several years.



## **DISCUSSION**

The experience of a provincial cancer program, the British Columbia Cancer Agency, over the decade 1972-1981 has been reviewed here in relation to cutaneous malignant melanoma. Patient referral to the BCCA is voluntary in contrast with provincial Cancer Registry notification which is mandatory. Potential referral bias would likely be against the referred group since treatments for advanced melanoma are almost exclusively available through BCCA.

During the study period, 76 patients were entered on a National Cancer Institute of Canada study of adjuvant immunotherapy. Ordinarily, the only cohorts of patients on whom outcome analysis is undertaken are those entered on clinical trials ; such patients have prospective data collection and periodic follow-up reports sent to the responsible clinical trial office. Assessment of clinical and pathological features, treatment and outcome in the remaining majority of patients must be undertaken retrospectively, as in this study.

The incidence of cutaneous malignant melanoma has risen progressively : in 1988, incidence rates for males and females were 11.5 and 12.8 per 100,000 respectively. It has been estimated that the lifetime risk of melanoma in the USA, where the current incidence is about the same as in British Columbia, will rise from 1:135 [1987] to 1:90 [2000]

{Balch, Houghton, Peters, 1985}. This alarming rise in incidence has been offset in part by a trend towards thinner melanomas [Bagley, Cady, Lee et al., 1981 : Balch, Shaw, Soong et al., 1985], confirmed in this study by increasing frequency of Clark levels I and II, and decreasing frequency of level V lesions. Depth comparisons by year of diagnosis were not possible because depth measurements were not regularly recorded in the early years of the present study. Interestingly, there was no observed decrease in primary tumor diameters at diagnosis over the decade of study. The net effect of increasing incidence and more frequent thin melanomas, however, is a slowly increasing death rate in the USA [Ries, Hankey, Edwards, 1990]. In British Columbia, melanoma mortality rates have increased minimally from 1974 to 1985.

The same investigative and reporting methodologies as have been used in many centres world-wide have been applied in the present series. Detailed discussion of the results has been presented in Chapters 2-4. Principal clinical and pathological features of all patients in the present study are consistent with most of the findings in clinical stage 1 melanoma from 14 centres [Balch, Soong, Shaw, 1985]. Specific characteristics of the present series were median age 47 years, females 53%, extremity primary 47%, lentigo melanoma 5%, superficial spreading melanoma 65%, T1 primary 31%, and primary ulceration in 25%. Ethnic origin is known to

affect melanoma risk, being lower in American blacks, and people of African, Asian and Mediterranean descent [Matas, 1896 : Crombie, 1979 : Feibleman and Maize, 1981], but was not recorded in the review process in the present series. The British Columbia population as a whole, however, is mostly of Caledonian origin.

The incidence of melanoma compared to other cancers is relatively low [BCCA, 1990]. In British Columbia, breast, prostate, lung and colorectal cancer incidences are much higher [98, 80, 47 and 35 per 100,000 in 1988]. Provincial cancer screening services are available for cancer of the cervix and, more recently, cancer of the breast. There are no plans for mass melanoma screening. Public awareness of melanoma in Canada is, however, increasing. The first week of June 1991 has been declared "Sun awareness week" by the Canadian Dermatology Association, which offers advice on sun exposure and protection and has called for closure of all indoor suntan studios. The present premier of the province of Quebec had a malignant melanoma of the trunk removed last year ; regular media reports raised awareness of melanoma.

A program of national education for the prevention of deaths from malignant melanoma has been proposed in the USA [Kopf, 1985 : Kopf, 1988] to include annual physical examination of the skin. The American

Cancer Society draws a subtle distinction between cancer screening [publicly funded] and early detection [individually funded] {Eddy, 1980} ; presently, annual examinations are the individual's responsibility.

In order to reduce the denominator of individuals screened for melanoma, the concept of a personal risk factor chart has been developed [Mackie, Freudenberger, Aitchison, 1989]. By identifying persons with many [>20] benign nevi, or with abnormal nevi, freckling tendency and history of severe sunburn, those at increased risk of developing melanoma could select themselves or be selected by their physicians for close surveillance and counselling.

During the analysis of the present study, it became apparent that more agreement is required among investigators in relation to reporting of results. In the review of prognostic factor analyses [Chapter 3], definition of variables and statistical methods were not consistent. It is quite possible that methodological differences in multifactorial analyses have contributed to the wide range of results and to some of the apparent geographic and biological differences in melanoma.

The present study of lymph node dissection has not yet influenced current treatment recommendations locally. From the National Cancer

Institute of Canada Immunotherapy study, the national elective lymphadenectomy rate for melanomas >0.75mm thick was about 20% [unpublished observation]. Most Canadian centres do not recommend ELND. Patterns of surgical practice change slowly and it appears that the local practice is unlikely to change until the results of the 2 current prospective randomised trials of ELND are available. On the positive side, however, the practice of recommending adjuvant BCG immunotherapy has been terminated as a result of the NCIC Trial.

The treatment of advanced unresectable melanoma continues to be an area of active research. The Physicians Data Query [PDQ] Base provided by computer link with the United States National Cancer Institute currently lists 44 phase I/II and 13 phase III studies of melanoma. The phase I/II studies range from investigation of "old" drugs [eg 6-thioguanine, suramin, regional melphalan], new drugs [eg toremifene, gemcytabine, lonidamine, merbarone, EDAM], combination chemotherapy [eg DTIC, tamoxifen, cisplatinum], biological response modifier therapy [eg regional interleukin 2 : alpha 2 interferon + interleukin : tumor-infiltrating lymphocytes + interferon] and monoclonal antibody therapy [eg anti-ganglioside R24 : anti-GD2 ganglioside : antibody MG-22 + interleukin 2]. Phase III studies include 6 adjuvant therapy trials and 5 chemotherapy +/- biological response modifier trials in metastatic disease. Such



investigational enthusiasm is, however, not shared by all oncologists. Observing that no disseminated neoplasm incurable in 1975 is curable today and that metastatic melanoma is "negligibly responsive" to chemotherapy, the practice of routine cytotoxic therapy or enrolment of all patients on clinical trials in metastatic melanoma has been questioned [Braverman, 1991]. Further research is however needed in the areas of tumor cell resistance, biological response modifiers and drugs with novel modes of action. At present, the best method of treating metastatic melanoma is to identify primary melanoma as early as possible and prevent the development of metastatic disease [Rhodes, Sober, Mihm et al., 1987 : Mackie, Freudenberger, Aitchison, 1989].

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# Primary Cutaneous Malignant Melanoma: Experience of the British Columbia Cancer Agency From 1972 to 1981

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A retrospective review of 891 patients with newly diagnosed primary cutaneous malignant melanoma (CMM) registered at the British Columbia Cancer Agency from 1972 to 1981 is presented. Age-standardized incidence rates in British Columbia have increased markedly over that time. The female-to-male ratio was 1.13:1 and the median age overall was 47 years. A change in the size of a mole was the most common presenting sign (in 43% of patients) and the median duration of signs was 5.9 months. Predominant tumour sites were the trunk for males and the lower limbs for females. Dominant growth patterns were superficial spreading melanoma (65%), nodular melanoma (25%), lentigo maligna melanoma (5%) and acral lentiginous melanoma (2%). On staging of the primary tumour, 90% of patients had local disease, 9% of patients had regional disease and 1% of patients had distant disease at presentation. Median depths of tumours were 1.45 mm for males and 1.10 mm for females; no T1 tumours (tumours 0.75 mm or less in depth [TNM classification]) were staged beyond the local area. Disease recurred in 44% of males and 32% of females. The 15-year survival rate was 55.5% for males and 70.3% for females. These findings are compared with those of recent international series. It is apparent that earlier diagnosis improves survival and that more education is needed in view of the increasing incidence and death from CMM.

On présente une étude rétrospective de 891 patients souffrant d'un mélanome cutané malin (MCM) primaire nouvellement diagnostiqué, enregistrés à l'Agence pour le Cancer de Colombie Britannique entre 1972 et 1981. Dans cette province, l'incidence corrigée pour l'âge a augmenté sensiblement au cours de cette période. Le rapport femmes / hommes a été de 1,13 pour 1 et l'âge médian de 47 années. Le signe le plus fréquemment observé était une augmentation de la taille de la môle (chez 43 % des patients) et la durée médiane des signes a été de 5,9 mois. Les foyers d'apparition des tumeurs primitives étaient le tronc pour les hommes et les membres inférieurs pour les femmes. Les caractéristiques tumorales dominantes ont été les mélanomes malins à extension superficielle (65 %), les mélanomes nodulaires d'emblée (25 %), les mélanomes sur mélanose de Dubreuilh (5 %) et les mélanomes lentigineux des extrémités (2 %). Lors du diagnostic, le stade évolutif des tumeurs primitives était le suivant : 90 % de tumeurs localisées, 9 % d'atteintes régionales et 1 % d'envahissements à distance. La profondeur médiane des tumeurs était de 1,45 mm pour les hommes et de 1,10 mm pour les femmes; aucune tumeur de stade T1 (d'une profondeur inférieure à 0,75 mm [classification TNM]) n'a été retrouvée au delà de la surface locale. La maladie est réapparue chez 44 % des hommes et chez 32 % des femmes. La survie à 15 ans a été de 55,5 % pour les hommes et de 70,3 % pour les femmes. Ces résultats sont comparés à ceux d'études internationales récentes. Il est évident qu'un diagnostic précoce améliore la survie et que, devant l'augmentation de la fréquence des MCM et de la mortalité qui lui est attribuable, une meilleure éducation du public s'impose.

Malignant melanoma represented 1.41% of all cancers in British Columbia in 1974, but by 1987 the incidence had increased to 3.11% for men and 3.7% for women.<sup>1</sup> Similar increases in melanoma incidence have been reported in the United States, Scandinavia and Australia.<sup>2-4</sup> This alarming increase has prompted many studies of risk and prognostic factors. These studies have suggested that the increase in incidence is real and not due to inadequate data,<sup>5</sup> artefacts of diagnosis or notification, or changes in "cosmetic factors."<sup>6-8</sup> Established risk factors include the presence of freckles<sup>9</sup> and benign nevi,<sup>10</sup> a his-

From the British Columbia Cancer Agency, Victoria Clinic, Victoria, BC

Presented at the 60th annual meeting of the Royal College of Physicians and Surgeons of Canada by the Canadian Association of Teachers of Community Health, Quebec, Que., Sept. 20, 1991

Supported in part by the British Columbia Cancer Foundation

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Accepted for publication Aug. 27, 1991

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tory of severe sunburn resulting in peeling,<sup>11</sup> exposure to ultraviolet light,<sup>12,13</sup> occupation and socioeconomic status.<sup>14-16</sup>

Many biologic factors influence the natural history of malignant melanoma,<sup>17</sup> including stage, histogenic or growth pattern, anatomic site of the tumour, age and sex. This report is a retrospective descriptive review of these factors in patients with primary cutaneous malignant melanoma (CMM) registered with the British Columbia Cancer Agency (BCCA) from 1972 to 1981.

## Patients and Methods

### Patients

From 1971 to 1981 in British Columbia the proportion of persons of British origin decreased from 58% to 51%.<sup>1</sup> Those of European ancestry increased from 18% to 27%, and the proportion of Asians increased from 2.6% to 4.5%. The higher proportion of inhabitants of British origin is significant in that persons of Celtic origin seem to have a higher incidence of malignant melanoma.<sup>4</sup>

Registration of malignant disease with the provincial cancer registry is mandatory for pathologists, but clinical referral to the BCCA is voluntary. The present study included all new cases of primary CMM diagnosed between June 1, 1972, and May 31, 1981, and registered with the BCCA. Follow-up extended to Apr. 30, 1990. In the defined period of this study there were 1944 persons in British Columbia registered with melanoma in the British Columbia Cancer Registry. Of these, 1245 (64%) patients were also registered with the BCCA. A list of cutaneous melanoma patients registered during the

study period was generated manually in 1983, and the 891 patients thereon formed the basis of this report. In 1990, an additional 198 patients were identified as having been registered in the study period, but these were not included.

A total of 27 patients had malignant melanoma in multiple sites at diagnosis. Primary malignant melanoma occurred on two separate occasions in 25 patients. These were counted only once in the incidence analysis.

### Data Collection

Data on 147 demographic, histopathologic, treatment and outcome variables were extracted from the medical records of the study population. Data were transcribed on to an abstract form and later computerized into a database (dBase IV) to facilitate follow-up and statistical analysis.

Histopathologic studies were performed at hospital laboratories throughout the province. The majority of the biopsies were reviewed by two BCCA pathologists in Vancouver. Growth patterns of the melanoma were described pathologically by the classification system used by Clark and associates.<sup>18</sup> The five main subdivisions of malignant melanoma used in this study were lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM), nodular melanoma (NM), acral lentiginous melanoma (ALM) and not otherwise specified (NOS).

Tumour depth was assessed by Clark's histopathologic method<sup>19</sup> and Breslow's micrometer measurement.<sup>20</sup> The study included cases antedating the universal usage of these methods. Depth measurements were not available for 223 (25%) patients and diameter measurements were unavailable for 102 (11%) patients. Depth categorization was determined from the "T"

category of the TNM classification system:<sup>21</sup> T1 (less than 0.75 mm), T2 (0.76 to 1.50 mm), T3 (1.51 to 3.0 mm) and T4 (greater than 3.0 mm). The *International Classification of Diseases*, 8th revision, was used to categorize primary sites.<sup>22</sup> Four principal categories were used: head and neck (H & N), trunk (T), lower limb (LL) and upper limb (UL). According to a modification of the M.D. Anderson Hospital system,<sup>23</sup> stage was categorized as local (stages I and II), regional (stage III) and distant (stage IV).

### Statistical Methods

Data were analysed by the Statistical Package for Social Sciences (SPSS-X release 3.1).<sup>24</sup> All percentages refer to total cases in the study population unless otherwise stated. Trends in incidence were analysed by simple linear regression analysis. The "utility test" model was used to test statistical significance of incidences between males and females. Means and standard deviations are all reported as mean  $\pm$  SD. Survival as a time interval was calculated from date of diagnosis to date of death, last written or physician contact. Statistical significance of differences between the sexes was tested by the Mann-Whitney U-test.

Age-standardized rates based on the number of tumours were adapted to those of the British Columbian population at the 1971 census by the direct method of standardization.<sup>25</sup> Mortality data were provided by the Division of Vital Statistics of the provincial Ministry of Health.<sup>1</sup> All population data were obtained from Census Canada publications.<sup>26</sup>

Survival curves were generated with the Kaplan-Meier product limit method<sup>27</sup> with the biomedical computer program BMDP.<sup>28</sup> The Tarone-Ware  $\chi^2$  test<sup>29</sup> was used to test the significance of gender on

survival. Cases with missing data were excluded from the relevant analysis procedures. Overall mean survival times were calculated using only survival times of cases with a response (death from melanoma).<sup>28</sup>

## Results

### Incidence and Mortality

Age-standardized incidences of malignant melanoma in British Columbia have increased significantly ( $p < 0.0001$ ) for both females and males (Fig. 1). In 1983, the age standardized death rate per 100 000 in Canada and British Columbia was 1.8.<sup>1</sup> The death rates associated with malignant melanoma in British Columbia did not change substantially for either men or women during the period 1974 to 1985 (Fig. 1).

### Clinical History

A change in the size of a mole was the commonest (43%) present-

ing sign. Other signs and symptoms were the development of a new mole (13%), a change in colour (9%), bleeding or ulceration (8%) and pain, tenderness or itching (8%) in a mole.

Bleeding or ulceration was a presenting sign in 4% of UL lesions, 8% of T lesions and 9% of H & N and LL lesions.

Development of a new mole was a presenting sign in 8% of T lesions, 14% of UL lesions, 16% of LL lesions and 20% of H & N lesions. Melanoma was recognized by a physician in 7% of patients who did not bring it to the physician's attention.

### Age and Sex Distribution

There were 472 females and 419 males, an overall female-to-male ratio of 1.13:1, but this was not constant over the study period. From 1972 to 1975 the ratio averaged 0.84:1 and from 1976 to 1981, 1.25:1. Patients' ages ranged from 9 to 99 years for males and from 3 to 93 years for females. Overall, the median age was 47

years and the mean age  $48.2 \pm 16.9$  years; for males, the mean age was  $49.7 \pm 17.4$  years, and for females the mean age was  $46.9 \pm 16.3$  years. The difference between the means was not significant.

### Times From First Sign or Symptom to Death

Median times from first sign or symptom to diagnosis were 5.6 and 6.2 months in males and females respectively. Females had longer median time from diagnosis to first recurrence (24.2 v. 19.7 months). Median times from recurrence to death were similar for females and male (10.9 and 11.6 months).

### Distribution by Age, Site, Growth Pattern and Stage

Table I illustrates the distribution of age, Clark's level, growth pattern and stage according to site and sex. Predominant sites were the trunk for males (46% [193 of 419] of the total male population) and lower limb for females (44% [206 of 472] of the total female population). T lesions occurred predominantly in patients under 60 years of age (81% [156 of 193] of all male and 86% [96 of 112] of all female T lesions). In contrast 48% (46 of 96) of all male and 44% (26 of 59) of all female H & N lesions occurred in patients over 60 years of age. The distribution of LL lesions was similar to that of T lesions: 74% (46 of 62) of LL lesions in males and 80% (164 of 206) of LL lesions in females occurred in patients under 60 years of age.

Overall there was little difference in the ages of patients for lesions at the major body sites except for the H & N where median ages were higher (Table II). Females had lower median ages for T and UL lesions.

The recorded distribution of specified growth patterns was SSM

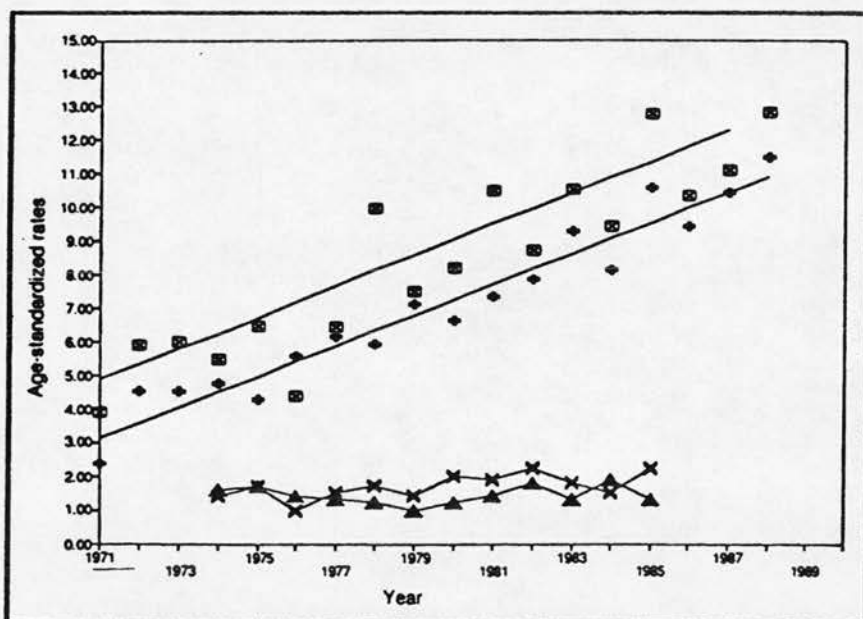


FIG. 1. Melanoma incidence by sex (+ = male, x = female) and mortality by sex (x = male, Δ = female) in British Columbia 1971 to 1988.

(65%), NM (25%), LMM (5%), and ALM (2%). Fig. 2 illustrates growth patterns by age. LMM proportions increased with age and occurred mainly on the H & N (80%). Only 13% of all LMMs occurred in patients under age 50 years of age. SSM proportions declined over age 60 years.

Staging information was complete in 870 cases: 90% had local disease, 9% had regional disease and 1% had distant disease. Regional lymph node dissection was performed in 282 patients and in 84 (29.8%) patients the nodes were found to contain malignant cells on histologic examination. The incidence of regional or distant disease according to the site of the primary lesion in the total staged population was 6.2% for UL lesions, 9% for T lesions, 11.8% for H & N lesions and 12.6% for LL lesions and ac-

cording to the site in males and females respectively was 14.7% and 7% for H & N lesions, 8.8% and 7.1% for T lesions, 5.2% and 7% for UL lesions, and 24.6% and 9.1% for LL lesions.

#### Distribution by Depth

Table III shows depth of invasion by sex according to age, site, growth pattern and stage. Overall the median depth was 1.20 mm (females 1.10 mm and males 1.45 mm).

The depth distribution of tu-

mours was 31% for T1 tumours, 29% for T2 tumours, 25% for T3 tumours and 14% for T4 tumours. Females made up 62% of patients with T1 lesions, 55% of those with T2 lesions, 52% of those with T3 lesions and 43% of those with T4 lesions. Males made up 69% of patients with T3 and T4 H & N lesions and 70% of patients with T3 and T4 T lesions. T1 and T2 tumours constituted 55% (59 of 107) of all H & N lesions, 57% (119 of 209) of all LL lesions, 61% (147 of 241) of all T lesions and 69% (77 of 111) of all UL lesions. Clark's

Table II. Mean (and Median) Ages (Years) at Time of Diagnosis of New Patients With Primary Cutaneous Malignant Melanoma According to Sex and Tumour Site

Sex	Site			
	Head and neck	Trunk	Upper limb	Lower limb
Male	58 (57.4)	46 (46.4)	48 (49.8)	48 (48.1)
Female	56 (54.5)	39.5 (42.5)	43 (47.1)	47 (46.7)

Table I. New Cases of Primary Cutaneous Malignant Melanoma According to Age, Clark's Level, Growth Pattern, Stage, Site and Sex

Groupings	Site								Total*
	Head and neck		Trunk		Upper limb		Lower limb		
	M	F	M	F	M	F	M	F	
Age, yr									
0 - 39	22	15	67	56	18	34	20	75	307
40 - 59	28	18	89	40	20	32	26	89	342
60 - 99	46	26	37	16	19	21	16	42	223
Total	96	59	193	112	57	87	62	206	872
Clark's level									
I	5	0	4	3	2	0	0	7	21
II	13	15	33	22	9	18	4	46	160
III	16	8	58	39	16	31	16	45	229
IV	37	19	74	35	23	26	27	84	325
V	10	10	6	2	2	4	9	9	52
Total	81	52	175	101	52	79	56	191	787
Growth pattern									
LMM	17	12	0	0	1	2	1	3	36
SSM	25	27	111	74	31	47	26	119	460
NM	30	7	40	20	7	17	19	37	177
ALM	1	0	0	0	4	4	5	2	16
NOS	21	11	35	18	13	14	10	35	157
Other	1	2	6	0	1	3	1	8	22
Total	95	59	192	112	57	87	62	204	868
Stage									
Local	81	53	176	104	55	80	46	189	784
Regional	12	4	15	7	2	5	15	19	79
Distant	2	0	2	1	1	1	0	0	7
Total	95	57	193	112	58	86	61	208	870

\*Missing data account for differences between total study population (891) and totals in different categories above.

LMM = lentigo maligna melanoma, SSM = superficial spreading melanoma, NM = nodular melanoma, ALM = acral lentiginous melanoma, NOS = not otherwise specified



levels were assessed in 88% of cases, and their distribution in relation to depth is shown in Fig. 3.

No T1 lesions had spread beyond the local area at the time of diagnosis. Regional metastases were pres-

ent in 2.5% of all T2, 11.3% of all T3 and 17.2% of all T4 lesions at the time of presentation.

Growth patterns indicate that both SSM and LMM tend to be thin lesions: 42% of SSMs and 62% of LMMs were T1 tumours. NMs were thicker lesions: 46% were T3 and 37% were T4. ALM was an infrequent growth pattern: 66% of ALMs were T3 and T4.

### Recurrence

Disease recurred in 38% of the total study population (32% of all females and 44% of all males). Five patients had recurrence 10 or more years after the initial diagnosis.

Recurrences were predominantly (54% of all first recurrences) in the regional lymph nodes. The frequencies of primary sites responsible for all first recurrences were as follows: T, 38%; LL, 25%; H & N, 22%; and UL, 13%. Of patients experiencing a first recurrence, 27% had recurrence in two sites, 16% in

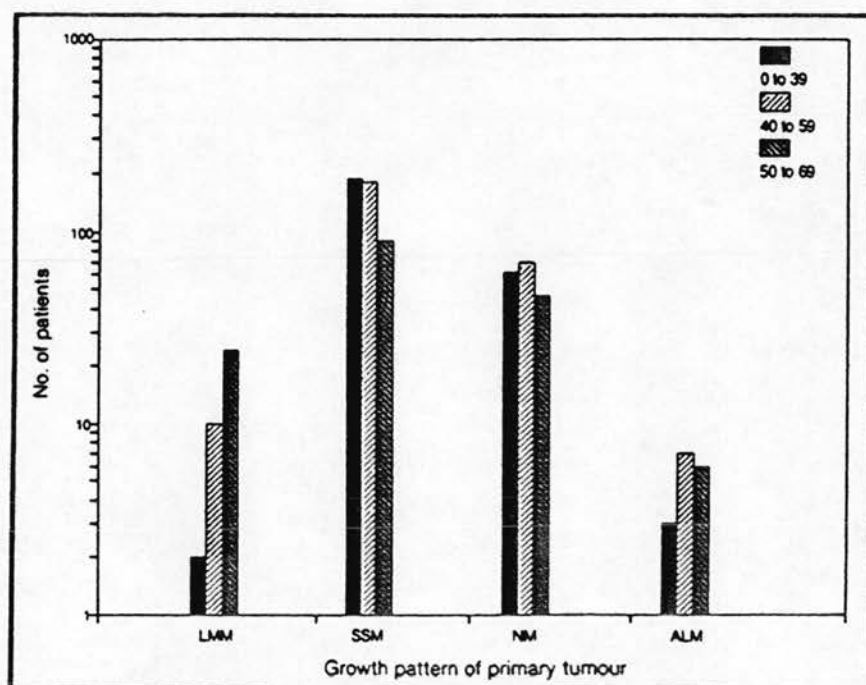


FIG. 2. Growth patterns of primary tumour by age (years). LMM = lentigo maligna melanoma, SSM = superficial spreading melanoma, NM = nodular melanoma, ALM = acral lentiginous melanoma.

Table III. Age, Site, Growth Pattern and Stage of New Cases of Primary Cutaneous Malignant Melanoma According to Depth of Invasion and Sex

Groupings	Depth of invasion*								Total†	
	T1		T2		T3		T4			
	M	F	M	F	M	F	M	F	No.	%
Age, yr										
0 - 39	31	54	19	47	33	40	12	11	247	37
40 - 59	31	55	45	37	29	36	20	15	268	40
60 - 99	18	19	23	23	19	12	23	16	153	23
Total,										
No.	80	128	87	107	81	88	55	42	668	100
%	12	19	13	16	12	13	8	6		100
Site										
Head and neck	17	17	15	10	14	9	19	6	107	16
Trunk	45	32	46	24	47	14	19	14	241	36
Upper limb	14	28	13	22	8	16	5	5	111	17
Lower limb	4	51	13	51	12	49	12	17	209	31
Growth pattern										
LMM	8	8	2	2	1	1	3	1	26	4
SSM	65	110	63	75	30	45	12	11	411	62
NM	0	1	12	12	33	32	30	22	142	21
ALM	1	0	1	2	3	1	2	2	12	2
NOS/other	6	9	9	16	14	9	8	6	77	12
Stage										
Local	80	128	84	105	72	78	44	36	627	94
Regional	0	0	3	2	9	10	11	6	41	6
Distant	0	0	0	0	0	0	0	0	0	0

\* TNM classification

† Total study population

three sites and 10.5% in four or more sites.

### Survival

Five-, 10- and 15-year survival rates were 68.9%, 58.2% and 55.5% for males and 82.9%, 74% and 70.3% for females ( $p \leq 0.0001$ ). Overall mean survival of those who died from CMM was 11.3 years for males and 13.7 years for females.

Malignant melanoma was the cause of death for 31% of the study population and accounted for 82% of all deaths. Of all patients who had a recurrence, 16% were disease free at last follow-up.

### Other Cancers

Thirty (3%) of the 891 patients had a previous basal cell cancer and 16 (2%) a squamous cell cancer. Other malignant tumours occurred in 48 patients (5%) before and 115 (13%) after the diagnosis of CMM.

Subsequent malignant tumours were mainly nonmelanoma skin cancers (66% of total subsequent malignant tumours).

### Discussion

CMM has been studied extensively over the last 20 years, seeking a better understanding of demographic, environmental, clinical and pathological factors. The increase in age-standardized incidence in Western developed countries has been well documented,<sup>30,31</sup> and a similar pattern was seen in this study. Melanoma incidence in several countries increased by 5% per annum in the 1960s and 1970s.<sup>32</sup> These increasing rates suggest that the trends observed are the results of true changes in risk. Data from the Surveillance Epidemiology and End Results Program<sup>33</sup> showed that the incidence in males exceeds that in females and is increasing at a

faster rate (4.8% per year compared with 3.6%); the death rates for males and females are increasing at 2% and 1.3% per year respectively. In our study the death rate for males exceeded that for females in 8 of the 9 years from 1977 to 1985, and overall survival for males was shorter for new patients registered from 1972 to 1981.

Data on sex, age, site and growth patterns have been compared with the findings of major series from the United States,<sup>34-38</sup> Canada,<sup>39</sup> New Zealand,<sup>40</sup> Scotland,<sup>41,42</sup> Denmark,<sup>43</sup> Australia<sup>44</sup> and Ireland.<sup>45</sup> This study's sex ratio was similar to those in all series except the one in Ireland and the two in Scotland, where the female-to-male ratios were 2.8:1, 1.9:1 and 2.17:1 respectively. All series except two in the United States<sup>35,36</sup> showed a female preponderance. The median age (47 years) of all patients in our study was virtually the same as those reported from Sydney and Alabama (48 and 44 years respectively).<sup>38</sup>

The commonest primary site in females in all studies has been the LL, accounting for 33% to 67% of all cutaneous melanomas. For males, the T was the commonest primary site (33% to 47%) in all studies except those in Ireland, Scotland and Rochester where the H & N was the commonest site. The findings in this study that 46% of all male melanomas were located on the T and 44% of all female melanomas were on the LL are consistent with the findings in most other series. A trend of increasing frequency of T melanomas and decreasing frequency of H & N melanomas in males has been reported from Sydney and Alabama<sup>38</sup> for the period 1958 to 1985.

In our study, the observed growth-pattern distribution was consistent with that of most previous reports. The most frequent (65%) growth pattern was SSM,

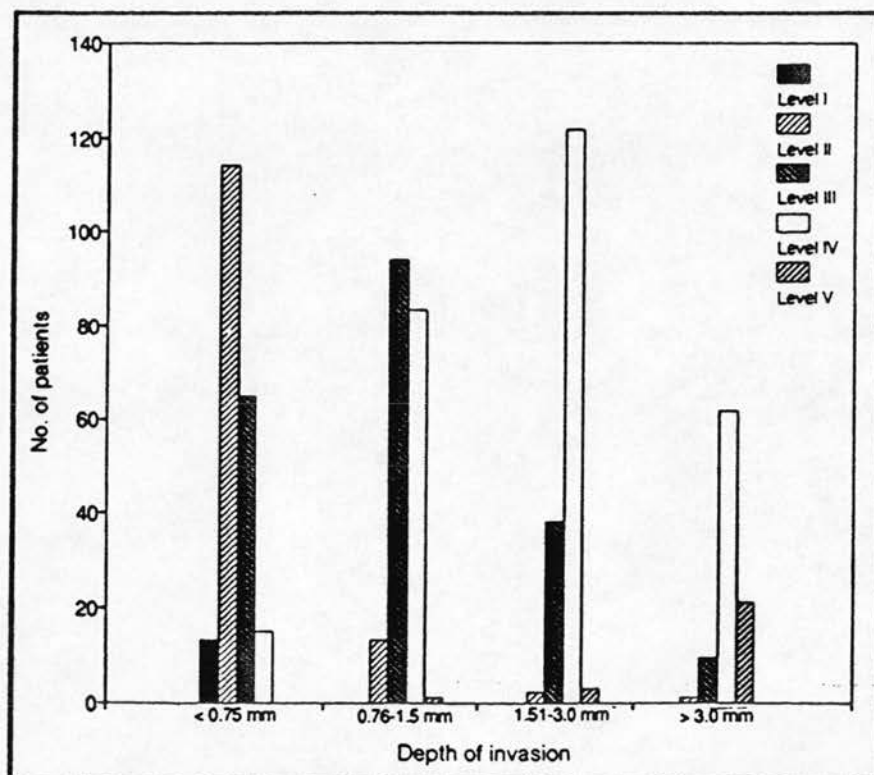


FIG. 3. Depth of invasion by Clark's level.

with NM and LMM accounting for 25% and 5% respectively. SSM is usually the most common growth pattern (51% to 73%), followed by NM (14% to 35%) with LMM between 4% and 9%. In Ireland, NM was the most common type, and LMM caused 18% of all melanomas in that series.<sup>45</sup>

Depth measurement by micrometer is now accepted as the most important indicator of prognosis.<sup>46</sup> The observations that 61% of the total population had primary tumours less than 1.5 mm in depth and that no T1 primary lesions were spread beyond the local area at diagnosis provide both encouragement and incentive to increase educational efforts toward earlier recognition and diagnosis of melanoma. Depth comparisons with other series are hindered by lack of standard reporting practices. In the series from Scotland for the period 1971 to 1976,<sup>41</sup> only 30% of patients had T1 and T2 tumours. In a worldwide comparative study,<sup>47</sup> 12% of patients had primary tumours more than 4 mm thick, and in our series 15% were more than 3 mm thick. In the combined experience of the Sydney melanoma group and the University of Alabama, median tumour thickness for males and females has decreased since the 1950s<sup>38</sup> to 1.4 and 1.2 mm, respectively, during the period 1976 to 1980. These median depths are close to those depths observed from 1972 to 1981 in our series (1.45 mm for males and 1.10 mm for females). Poorer prognoses in NMs<sup>46</sup> are related to their depth. For example, 83% of NMs but only 24% of SSMs were T3 or T4 in our series. ALM is also usually a deep lesion, 66% being T3 or T4 in our series.

The poorer prognosis of malignant melanoma in males is well documented<sup>46</sup> and has been confirmed here. The sex difference in

survival in the present study could be due to several factors: the generally thicker and larger volume tumours in males, the predilection to T and H & N lesions, the majority of thick lesions at those sites, the majority of regional or metastatic disease in all sites except UL at presentation and a tendency to shorter disease-free intervals from diagnosis to recurrence. The role of hormonal factors in the etiology and natural history of melanoma has been recognized and investigated for over 40 years,<sup>48</sup> but this association has yet to be successfully exploited therapeutically.

Most series report that the majority of patients have stage I disease at presentation, consistent with the findings in our series. Correlation of primary sites with potential metastatic disease at diagnosis according to sex showed that males had about twice the likelihood of regional or metastatic disease with H & N primary lesions than females, and almost three times the likelihood with LL primary tumours. An analysis of the elective and therapeutic lymph node dissections that were performed in this series appears elsewhere in this issue (pages 600 to 604).

The pattern of recurrent disease in melanoma is now well known. The disease-free interval is directly related to the depth of the primary lesion.<sup>49</sup> Regional lymph nodes are the commonest site of first metastases. In this series, 54% of first recurrences were in regional nodes. Elective lymph node dissection is known to be associated with a different pattern of metastatic disease, that is, fewer regional metastases (down from about 60% to 5%) and a proportional increase in other sites.<sup>50</sup> The prognostic importance of the development of recurrent disease is very clear from this series. Only 16% of patients experiencing recurrence were free of dis-

ease at last follow-up. New treatments are urgently required for this group of patients.

Several factors must be taken into account when comparing survival of patients between series.<sup>47</sup> Referral-centre results differ from population-based studies. Results from the last decade may be superior due to earlier diagnosis. The distribution of tumour thickness must be considered. Patterns of surgical practice, especially the rate of elective lymph node dissection will have a significant effect on staging and possibly on ultimate survival. Relapse is less likely in patients with pathological than with clinical stage I disease. In our series, 5-year survival rates of 68.9% and 82.9% for males and females (10% of whom had regional or distant metastases at diagnosis) compare favourably with those from other centres in which 5-year survival rates for stage I melanoma ranged from 62% to 81% and 70% to 100% in males and females respectively.

Early diagnosis is the best available method of improving survival in CMM. Since CMM can be found readily by self-inspection, the median time to diagnosis can be shortened with patient education. A public-health education program in Queensland has resulted in an increase in the number of thin tumours registered.<sup>51</sup> Awareness of warning signs in a mole — asymmetry, border irregularity, colour variegation and diameter (over 6 mm) or the ABCD of melanoma<sup>52</sup> — must be emphasized along with assessment and surveillance of individuals with dysplastic nevus syndrome or family members with melanoma, or both.<sup>53,54</sup> Public campaigns and further research aimed at early detection and treatment should reduce melanoma mortality, especially in areas of higher incidence such as British Columbia.



We thank Dr. Stephen Ashwell and Dr. David Lister for data collection, Mr. John Spinelli and Mr. Richard Gallagher, Department of Epidemiology, British Columbia Cancer Agency, for data transformation and consultation and Dr. P. Fisher, School of Health Information Science, for editorial contributions.

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## 1044

PRELIMINARY ANALYSIS OF A PHASE IB STUDY OF INTRALYMPHATIC AND SUBCUTANEOUS IL-2 IN PATIENTS WITH LOCAL AND REGIONAL METASTASIS IN MELANOMA. N.Yeilding, J.Kirkwood, D.Vlock, A.Zajko, J.Bryant, A.Roth, M.Gemperlein-McQueen, R.Herberman, T.Whiteside. Depts of Medicine and Pathology, University of Pittsburgh/Pittsburgh Cancer Institute, Pittsburgh, PA 15213.

We report the preliminary immunologic analysis and toxicity profile of a Phase Ib trial of low-dose intralymphatic and subcutaneous IL-2 for patients (pts) with loco-regional metastatic melanoma. Pts with *in transit* melanoma of an extremity (alone or accompanied by N1-N2) received IL-2 at 1.5 x 10<sup>6</sup>, 1.5 x 10<sup>6</sup>, 1.5 x 10<sup>6</sup>, or 1.5 x 10<sup>7</sup> Cetus U/M<sup>2</sup>/wk at 3 wk intervals by intralymphatic (IL) infusion the first course, then intradermally TIW or TID x 5 days for the second and third courses, respectively. In six pts who have been treated in the first two dosage tiers, one complete response (CR) (7+ mos) was seen, two pts had stable disease (28+ and 19 mos), and 3 pts had progressive disease. No dose-limiting toxicity was seen. All pts experienced mild to moderate pain and edema at the injection site; 4/6 pts experienced mild to moderate fatigue; and one pt developed mild hypotension responding to fluids. Immunologic parameters were analyzed x 3 prior to treatment and serially thereafter. Overall, no consistent changes related to treatment have yet been observed in the analysis of PBL phenotype, NK or LAK activity, or mitogens or alloantigen response, or serum levels of IL-2, IFN, TNF, or the soluble IL-2 receptor. The patient achieving a CR was noted to have increases in PBL DR expression and DR/Leu 2a co-expression and an increase in serum levels of TNF following IL-2 injection. Accrual to higher dosage tiers is currently in progress. We conclude that loco-regional administration of IL-2 at low dosages produces minimal toxicity and is associated with clinical responses. Accrual of additional patients may be needed to demonstrate effects on systemic immune parameters. Regional assessment of immunologic parameters may be more informative in the analysis of mechanisms of IL-2. (Supported by the Pardee Foundation)

## 1046

SEQUENTIAL CHEMOIMMUNOTHERAPY FOR METASTATIC MELANOMA. JM Richards, E Priest, V Hamasaki, P Skosey, K Ramming. University of Chicago, Chicago, IL 60637

Since February 1990 we have evaluated a sequential chemoimmunotherapy (CITx) for the treatment of metastatic melanoma. A cycle of therapy consisted of: BCNU (150 mg/m<sup>2</sup>) on day 1, DTIC (220 mg/m<sup>2</sup>) and CDDP (25 mg/m<sup>2</sup>) on days 1-3 and 22-24, interleukin-2 (IL-2) (1.5 mU/m<sup>2</sup> every 8 hrs) and alpha-interferon (αIFN) (6mU/m<sup>2</sup> sc once daily) on days 4-8 and 17-21, and tamoxifen 10 mg po twice daily for 6 weeks. Patients were evaluated for response 2-3 weeks after completing each cycle of therapy. Thirty-nine patients have been entered into this trial as of Dec. 1, 1990, and 25 have completed at least 1 cycle of therapy and have been evaluated for response. The best response are as follows:

Response	No.	Percent
Complete	6	24
Partial	9	36
Minor	1	4
Stable	8	32
Progressive	1	4

Median response duration has not been reached and is greater than 5 mos. Immunologic alterations associated with response will be presented.

## 1045

A PHASE IB TRIAL OF MURINE MONOCLONAL ANTIBODY R<sub>34</sub> (ANTI-GD3) IN METASTATIC MELANOMA. J. Raymond, J. Kirkwood, D. Vlock, M. Rabkin, R. Day, T. Whiteside, R. Herberman, R. Mascarini, and B. Simon. University of Pittsburgh/Pittsburgh Cancer Institute, Pittsburgh, PA 15213

R<sub>34</sub> reacts with the disialoganglioside GD3 found in a majority of melanomas, and mediates antibody dependent as well as complement dependent cytotoxicity against melanomas *in vitro*. Initial clinical trials against melanoma have revealed clinical responses at a range of doses of antibody. We have initiated a phase Ib trial of R<sub>34</sub> at dosages of 8-640 mg/M<sup>2</sup> to further evaluate antitumor activity and the optimal immunomodulatory dosage in subjects with metastatic melanoma. Five dose tiers of 6 pts each are planned. To date, 12/30 pts (8 F/4 M; age 25-73) have completed treatment on dose tiers I and II (8 and 80 mg/M<sup>2</sup>) given as a continuous IV infusion x 8 d. 2 pts with response in tier I have received maintenance therapy at half the initial dosage q 6 wk. Toxicity has included gr I-II flu-like syndrome, anemia, nausea/vomiting, and peritumoral pain, erythema, and edema. Two pts have experienced gr II-III volume overload. 3/6 pts in tier I and all above tier I have had urticaria. Chemical pancreatitis was noted in 1 pt. There have been no gr 4 toxicities, or anaphylaxis. Tumor response observed in 2 pts on tier I is notable: one developed 70% response following the initial infusion, regrowth of tumor to near-baseline and repeated response to maintenance at 6 and 12 weeks. Another achieved partial response to initial treatment, and entered complete response after maintenance x 2 cycles. Clinical evidence of response to R<sub>34</sub> in this trial includes regression in 2/6 subjects at the lowest dose tested, and tumor pain, edema, erythema and urticaria that suggest an immune mechanism. It is too early to correlate laboratory immune assessment and clinical responses in this study.

## 1047

CUTANEOUS MALIGNANT MELANOMA: BRITISH COLUMBIA CANCER AGENCY EXPERIENCE FROM 1972 TO 1981. K. S. Wilson, V. E. Carmichael. B.C. Cancer Agency Victoria Clinic, Victoria, B.C. V8R 1J8, and School of Health Information Science, University of Victoria, Victoria, B.C. V8W 3P5.

A retrospective review of 891 patients with newly diagnosed cutaneous malignant melanoma (CMM) registered at the B.C. Cancer Agency from 1972 to 1981 is presented. Age standardized incidence rates in B.C. have increased significantly over that time. Sex ratio was 1.13:1 in favor of females and median age was 47 years. Change in size of a mole was the most common presenting symptom and median duration of symptoms was 5.9 months. Predominant primary tumour sites were trunk for males and lower limb for females. Dominant growth patterns were superficial spreading melanoma (65%), nodular melanoma (25%), lentigo maligna melanoma (5%) and acral lentiginous melanoma (2%). Staging of the primary tumour was 90% local, 9% regional and 1% distant disease at presentation. Median depths of primary tumours were 1.45 mm for males and 1.10 mm for females. No T1 tumours (tumours ≤0.75 mm) were staged beyond the local area. Disease recurred in 44% of males and 32% of females. Fifteen year survival was 55.5% for males and 70.3% for females. These findings have been compared with other recent international series. It is apparent that earlier diagnosis improves survival and that more education is needed in view of the increasing incidence and mortality from CMM.



# Elective and Therapeutic Regional Lymph Node Dissection for Cutaneous Malignant Melanoma: Experience of the British Columbia Cancer Agency, 1972 to 1981

Vicki E. Carmichael, BSc;\* R. Edward Robins, MD, FRCSC;†  
Kenneth S. Wilson, MB, ChB, FRCP (Edin), FRCPC, FACP‡

The authors present a 10-year review of patients registered at the British Columbia Cancer Agency (BCCA) who underwent lymph node dissection for malignant melanoma. Pathological findings in the regional lymph nodes were correlated with primary site, growth pattern, depth of invasion and Clark's level. Elective lymph node dissection (ELND) was performed in 223 patients, and the overall positivity rate (pathologically involved nodes) was 16%. Survival rates for patients who had ELND were compared with those for BCCA patients not having had ELND and patients from the University of Sydney, Sydney, Australia. Although patients who underwent ELND had thicker and more frequently ulcerated primary tumours than patients with stage I disease who did not undergo ELND, survival was better in the group who had ELND. However, when all potential prognostic factors were analysed by multivariate analysis, ELND was not a significant factor in prognosis.

Therapeutic lymph node dissection (TLND) was performed in 50 patients at the time the primary tumour was diagnosed, and involvement of the lymph nodes was found in 36. Of 525 patients with clinical stage I disease who did not have ELND, disease recurred in the regional lymph nodes in 119; 86 of them had TLND for recurrence (RTLND). Median survival rates from the time of diagnosis of the primary lesion for ELND-positive, TLND-positive and RTLND patients were 4.2, 2.7 and 4.4 years respectively; the differences were not significant. New treatments are required for patients with involved regional lymph nodes.

Les auteurs décrivent les résultats d'une étude d'une durée de 10 ans portant sur les patients de l'Agence pour le Cancer de Colombie Britannique (ACCB) qui subirent une dissection ganglionnaire pour un mélanome malin. Les constatations des examens pathologiques ont été reliées au foyer primaire, aux caractéristiques de croissance, à la profondeur et au niveau selon la classification de Clark. Une dissection ganglionnaire non urgente (DGNU) fut pratiquée chez 223 patients et le taux d'examen positifs fut de 16 %. Le taux de survie des patients qui subirent une DGNU a été comparé à celui des patients de l'ACCB qui ne subirent pas de DGNU et à celui des patients de l'Université de Sydney, Sydney, Australie. Même si les patients qui subirent une DGNU avaient des tumeurs plus profondes et plus fréquemment ulcérées que les patients de stade I qui n'eurent pas de DGNU, la survie fut meilleure dans le groupe DGNU. Néanmoins, l'analyse multifactorielle de tous les facteurs pronostiques possibles n'a pas fait ressortir la DGNU comme facteur pronostique déterminant. Une dissection ganglionnaire thérapeutique (DGT) fut effectuée chez 50 patients au moment du diagnostic primaire et une atteinte ganglionnaire fut constatée chez 36 d'entre-eux. Des 525 patients au stade clinique I qui n'eurent pas de DGNU, une récurrence ganglionnaire régionale survint chez 119; de ce groupe, 86 subirent une DGT pour récurrence (DGTR). Les survies médianes à partir du diagnostic de la lésion primaire pour les patients DGNU-positifs, DGT-positifs et DGTR furent de 4,2, 2,7 et 4,4 années, respectivement; la différence n'est pas statistiquement significative. Il existe un besoin de thérapies nouvelles pour les patients souffrant d'atteintes ganglionnaires régionales.

The role of surgery in removing clinically malignant or equivocal regional lymph nodes (therapeutic lymph node dissection [TLND]) either when the diagnosis of primary malignant melanoma is made or subsequently for recurrence (recurrent therapeutic lymph node dissection [RTLND]) is firmly established.<sup>1</sup> However, the survival benefit of removing clinically normal regional lymph nodes as soon as the primary lesion is diagnosed (elective or prophylactic lymph node dissection [ELND]) is controversial.<sup>1</sup>

Since 1976, the Melanoma Tumour Group of the British Columbia Cancer Agency (BCCA) has recommended ELND for patients with "high-risk" clinical stage I malignant melanoma, defined as those with primary tumour of Clark's level III and depth of dermal inva-

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Presented at the 14th annual meeting of the Canadian Association of General Surgeons, held in conjunction with the 60th annual meeting of the Royal College of Physicians and Surgeons of Canada, Quebec, Que., Sept 20, 1991

Supported in part by the British Columbia Cancer Foundation

Accepted for publication Oct. 9, 1992

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sion greater than 0.76 mm, those with Clark's level 4 or 5, and those in whom one anatomic lymph node drainage site could be identified. This recommendation was modified in 1983 to stage I patients with tumours more than 1.5 mm deep. In this study we report the BCCA experience with ELND, TLND and RTLND for malignant melanoma. Factors influencing the ELND positivity rate are presented. Survival in patients who had ELND is compared with that of a concurrent control group of clinical stage I patients who, in the same decade, were treated without ELND (designated BCCA control patients), and with that of other series. Reasons for omitting ELND included patient and referring surgeon's decisions in the light of possible expected benefits. The effect of ELND on survival of all patients with clinical stage I malignant melanoma who were registered at the BCCA during the study period and were treated by wide primary excision has been analysed by multifactorial analysis according to whether or not they underwent ELND.

### Patients and Methods

In 1983 we began a retrospective review of all patients who had registered at the BCCA with malignant melanoma between June 1, 1972, and May 31, 1981.<sup>2</sup> The records of 891 patients were reviewed, and all of those who underwent ELND, TLND and RTLND and BCCA control patients (vide supra) form the basis of this report. Lymph node dissection for cure was performed by referring surgeons throughout the province.

The data were analysed with the Statistical Package for Social Sciences (SPSS-X, release 3.1).<sup>3</sup> Survival was analysed by the product limit method. Multifactorial analysis was undertaken with the Cox pro-

portional hazards model. Differences between survival curves were calculated with the log rank test.

### Results

#### ELND

ELND was performed in 223 patients, 104 male and 119 female. In patients with specified negative clinical evaluation of regional nodes, ELND was pathologically positive in 19 (18%) males and 16 (13%) females for a combined positivity rate of 16%. ELND positive and negative frequencies and overall percent positivity according to site and growth pattern of the primary tumour, depth of invasion and Clark's level are summarized in Table I.

Depth measurements were available in 202 patients who underwent ELND. Median depths of primary tumours in ELND-positive and ELND-negative patients were 3.0

mm and 1.6 mm respectively. Median depth of primary tumours was greater in all patients who had ELND (1.64 mm) than in 530 BCCA control patients (1.00 mm) ( $p < 0.0001$ ). Site distribution of the primary tumour in patients who had ELND and in BCCA control patients was 20% and 17% (upper limb), 41% and 25% (lower limb), 26% and 41% (trunk), and 13% and 18% (head and neck). Primary ulceration was present in 53% of patients who had ELND and in 20% of BCCA control patients. In patients with positive ELND, 18 had one positive node, 7 had two positive nodes and 7 had three or more positive nodes; 3 patients had an unspecified number of positive nodes. The number of positive nodes made no significant difference to the patient's survival. Disease recurred in 27% (50 of 188) of the ELND-negative patients. There were 23 (66%) recurrences in the 35

Table I. Characteristics of Patients With Pathologically Positive and Negative Nodes on Elective Lymph-Node Dissection (ELND)

Characteristics	ELND positive	ELND negative
Sex		
Male	19	85
Female	16	103
Site of primary		
Upper limb	3	41
Lower limb	16	77
Head and neck	4	24
Trunk	12	46
Growth pattern		
SSM	16	102
NM	14	57
LMM	0	1
ALM	0	4
NOS	5	24
Depth of invasion of primary tumour*		
T1	0	15
T2	5	67
T3	12	67
T4	13	24
Unspecified	5	15
Clark's level		
II	0	4
III	3	65
IV	24	108
V	6	7

SSM = superficial spreading melanoma, NM = nodular melanoma, ALM = acral lentiginous melanoma, LMM = lentigo maligna melanoma, NOS = not otherwise specified

\*TNM classification

ELND-positive patients. In these patients the median survival was 4.2 years, and 37% of them survived 10 years. Median survival of ELND-negative patients has not been reached (Fig. 1).

Ten-year disease-specific survival rates according to depth and level of invasion of the primary tumour in BCCA control patients and those who had ELND are shown in Figs. 2 and 3. Survival differences were significant in favour of patients who had ELND when grouped according to either level or depth of invasion ( $p < 0.0001$ ). In patients with a T2 primary tumour, the group with the largest difference in survival (23%), only five (7%) had pathologically positive lymph nodes out of a total of 72 dissections.

Univariate and multivariate analysis of survival was undertaken in 720 clinical stage I patients. Of these patients, 192 had local excision (LE), 3 had LE and ELND, 327 had wide excision (WE) (more than 5 cm total width) and 198 had WE and ELND. Ten-year disease-specific survival rates for patients who

underwent the various types of surgical excision were 38% for those with LE, 50% for those with LE and ELND, 67% for those with WE and 67% for those with WE and ELND.

Multivariate analysis did not show ELND to be a significant factor determining prognosis. Univariate analysis showed that patients having only LE had significantly poorer

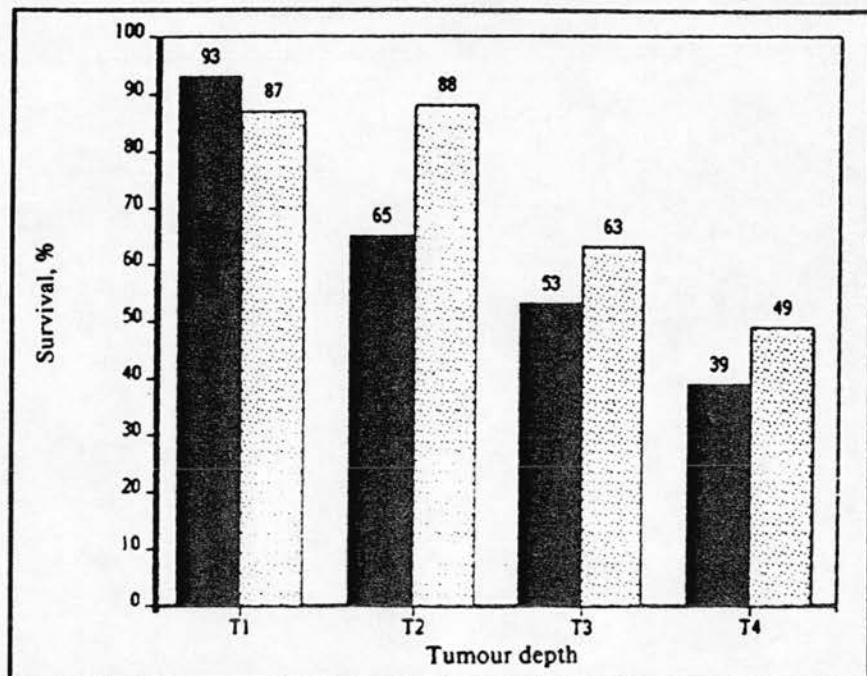


FIG. 2. Ten-year disease-specific survival rates in patients with malignant melanoma registered with British Columbia Cancer Agency (BCCA) according to depth of primary tumour. Solid bars = no ELND, dotted bars = ELND.

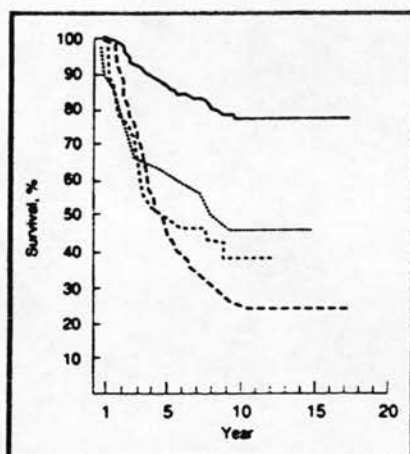


FIG. 1. Ten-year disease-specific survival rates in patients with negative elective lymph node dissection (ELND) (solid line), positive ELND (short dashed line), positive therapeutic lymph node dissection (TLND) (dotted line) and therapeutic lymph node dissection for recurrence (RTLND) (long dashed line).

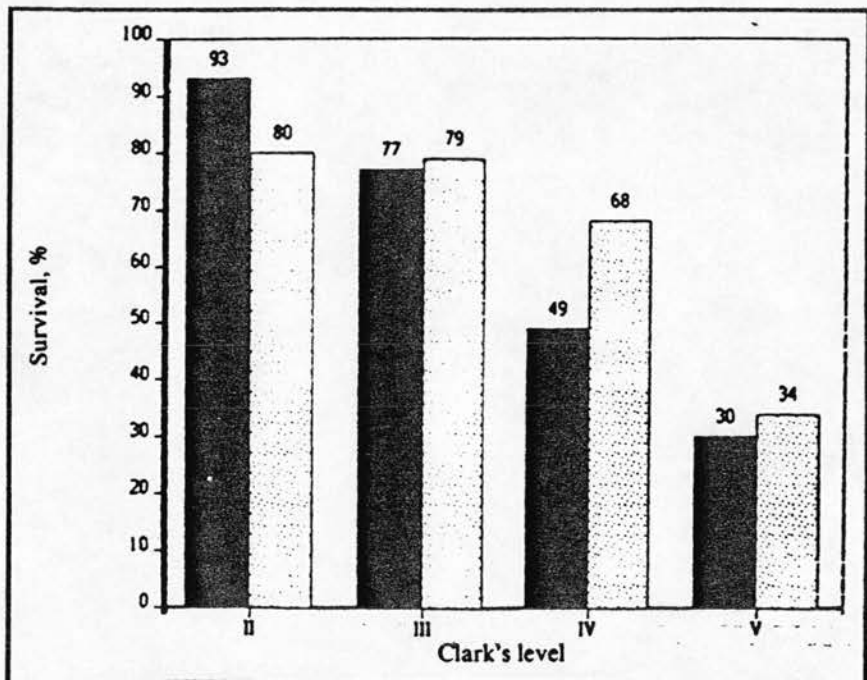


FIG. 3. Ten-year disease-specific survival rates according to level of invasion of primary tumour. Solid bars = no ELND, dotted bars = ELND.



survival, and multivariate analysis showed this to be significant as well ( $p = 0.0015$ ).

Three subgroups of patients were identified in the present series to allow comparison of outcome in patients who appeared to benefit most from ELND in the University of Sydney series, that is, males with T3 trunk primaries and males and females with T3 extremity primaries.<sup>4</sup> Ten-year survival rates for four groups of patients are shown in Fig. 4. The groups were University of Sydney patients and BCCA patients who had ELND and University of Sydney patients and BCCA patients who did not have ELND. Patient numbers for each of these groups were 81, 19, 104 and 26 (T3, male, trunk); 55, 11, 61 and 4 (T3, male, extremity); 71, 41, 135 and 18 (T3, female, extremity). Survival differences between the two cohorts of BCCA patients — those who had ELND and control — for

these specific sex and primary-site groups were not significant ( $p = 0.1175$ ). The numbers of patients in the BCCA ELND groups were small, especially male patients with T3 extremity primary tumours. Survival rates for all BCCA patients in these categories were intermediate between the University of Sydney patients who did not have ELND and those who did.

#### TLND

TLND was performed in 50 patients at the time the primary tumour was diagnosed, and 36 (24 males and 12 females) had pathologically positive nodes. Of these 36 patients, 12 had one positive node, 3 had two positive nodes, 12 had three or more positive nodes and 9 had an unspecified number of positive nodes. The median depth of the primary tumour was 2.0 mm. Disease recurred in 24 (67%) patients

with positive nodes, and median survival was 2.7 years. The 10-year survival rate was 45%.

#### RTLND

Of 525 clinical stage I patients who did not have ELND, 119 (70 male and 49 female) had regional lymph node recurrence. RTLND was performed in 86 of these patients. The median depth of the responsible primaries in these patients was 2.3 mm. The site distribution of these primary tumours was 47% in the trunk, 21% in the lower limb, 18% in the head and neck and 14% in the upper limb. Median time to regional lymph node recurrence from primary treatment was 1.4 years. For all RTLND patients the median survival was 1.8 years from the date of recurrence and 4.4 years from the date of primary-tumour diagnosis. Ten-year survival was 26%. Survival curves for ELND-positive, TLND and RTLND patients (Fig. 1) were not significantly different ( $p = 0.82$ ).

#### Discussion

The role of ELND in the surgical management of cutaneous malignant melanoma has been extensively studied in both nonrandomized and randomized clinical trials.<sup>1</sup> Results of two randomized trials did not confirm the apparent benefits seen in nonrandomized studies, but reanalysis of the World Health Organization (WHO) Trial suggested that a subgroup of patients at intermediate risk of recurrence had a superior survival with ELND.

The rationale for ELND is based on the hypothesis that microscopic metastases may disseminate sequentially from primary to regional lymph nodes to distant sites and that removal of nodal micrometastases will prevent the development of incurable distant metastases.<sup>5</sup>

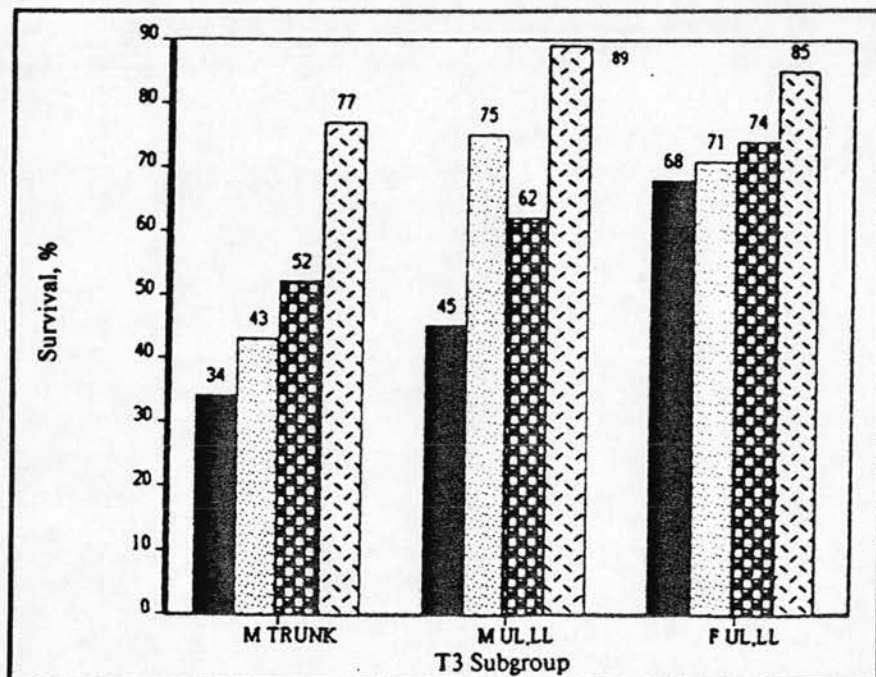


FIG. 4. Ten-year disease-specific survival rates in patients with T3 primary malignant melanoma registered with BCCA and from University of Sydney, Sydney, Australia, according to sex, site of primary tumour and whether or not ELND was performed. Black bars = Sydney series, no ELND; dotted bars = BCCA series, no ELND; cross-hatched bars = Sydney series, ELND; chequered bars = BCCA series, ELND. M = male, F = female. UL = upper limb, LL = lower limb.

The present study confirms the high subsequent death rate in patients with lymph node positive melanoma. We were unable to show, however, that patients who had pathologically positive nodes on ELND had a better survival than patients who underwent either TLND or RTLND. We confirm the finding of a previous report that the number of positive nodes in patients who had ELND is not significant for survival.<sup>6</sup> However, if the number of positive nodes is expressed as a percentage, some patients with ELND (those in whom the depth of invasion of the primary tumour was less than 3.5 mm and less than 20% of the nodes were positive) have a good prognosis (i.e., 66% 7-year survival).<sup>7</sup>

The yield (percent probability of detecting lymph node metastases) of ELND in this study (16%) is within the range (4% to 25%) of previous reports.<sup>4,8</sup> Yields according to depth of the primary tumour are also consistent with those of previous reports: 5% to 10% for T2, 17% to 20% for T3 and 39% for T4 tumours.<sup>9</sup> Interestingly, the series with the lowest reported overall yield (4%) showed the largest apparent treatment effect of ELND. Some patients in the group with pathologically negative nodes on ELND may in fact be those who are likely to benefit most from the procedure. In the present series, the yield in patients with the largest survival difference (T2 primary tumours) was only 7%. Most studies, including ours, have reported higher lymph node relapse rates in patients who did not have ELND than the yield at ELND, suggesting that some patients have lymph node metastases that are not identified at ELND.<sup>8</sup>

Survival of BCCA patients who had ELND has been compared with BCCA control patients and patients from the University of Sydney with

melanoma of the trunk and extremities. Although depth of invasion among BCCA patients who had ELND was significantly greater and primary ulceration was more frequent than in concurrent BCCA control patients, 10-year survival rates were significantly better, especially for T2 and Clark's level IV primary tumours. However, Clark's level IV primary tumours accounted for 43% of T2 primaries, and, conversely, T2 primaries accounted for only 29% of Clark's level IV primary lesions.<sup>2</sup> These figures suggest that factors other than ELND contribute to the survival differences. BCCA patients who had ELND had more favourable primary sites, more lower limb primaries and fewer trunk and head-and-neck primaries. In addition, ELND was performed only when a single lymphatic drainage area was present, not in patients with midline or watershed primary tumours.

The results of multifactorial analysis in patients with clinical stage I melanoma in our series showed that ELND was not an independently significant factor for survival. Nor was there any significant benefit for patients in the three groups of T3 primary melanomas who appeared to benefit in the report from the University of Sydney.<sup>4</sup> The analysis of survival after ELND according to tumour depth showed the largest difference in patients with T2 primary tumours, a group for whom we currently do not recommend ELND.

The role of ELND in any subgroup of clinical stage I melanoma remains uncertain. Ultimately, further prospective randomized trials are required to define the therapeutic role of ELND. There are two current prospective randomized trials addressing the role of ELND. An American intergroup study has included patients with intermediate-thickness (1 to 4 mm) melanoma of

the trunk and extremities. The WHO Melanoma Group is studying trunk primary melanomas greater than 2 mm thick.

Median survival rates for patients with positive nodes on ELND and TLND and patients who had RTLND in the present series compare favourably with those of previous reports.<sup>6,10,11</sup> However, all the results confirm the need for new treatments in patients with lymph node positive melanoma.

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# Analysis of prognostic factors in clinical stage 1 cutaneous melanoma

By Vicki Carmichael, BSc, Roger R. Davidson, PhD and Kenneth S. Wilson, BSc, MBChB, FRCPC

Clinical records of 753 patients with clinical stage 1 cutaneous malignant melanoma registered at the British Columbia Cancer Agency (BCCA) between 1972-81 were reviewed. Multivariate analyses utilizing appropriate subsets of 28 clinical and pathological variables showed that logarithm of micrometer depth, Clark level, pathological ulceration, primary site, type of initial surgery, growth pattern, and lymphatic invasion were the principal prognostic factors. This retrospective study compares the BCCA results with previous reports worldwide.

## Introduction

The likelihood of recurrence after surgery for stage 1 primary melanoma can be assessed with reasonable accuracy in most patients. Of all clinical and pathological variables in primary cuta-

neous melanoma, depth of invasion measured by micrometer has been found to be most consistently and strongly associated with risk of recurrence and death from melanoma.<sup>1</sup> The present study is part of a retrospective review of cutaneous malignant melanoma registered with the BCCA between 1972-81.<sup>2</sup> Survival analysis according to 28 clinical and pathologic factors was undertaken.

## Patients and methods

Medical records of 796 patients with clinical stage 1 cutaneous malignant melanoma referred to the BCCA from 1972-81 were reviewed. Clark level I patients and those with "borderline melanoma" were excluded from analysis because of 100% survival. Follow-up data was missing in seven cases, leaving a total of 753 cases for analysis. Definition of most variables has been reported previously.<sup>2</sup> BANS sites refer to primary tumors on the upper back, posterior aspect of upper arms, posterior neck and scalp. The posterior up-

per arm and upper back were not coded separately in the present series. This report utilizes posterior upper extremity and posterior trunk instead ("modified" or mBANS sites). Wide excision (WE) was defined as >5 cm skin in the re-excision specimen; all excisions of lesser dimensions were designated local (LE).

The principal study objective was to evaluate survival from melanoma in relation to 28 clinical and pathological factors. Observation times for patients leaving the study for reasons other than death from melanoma, and for patients alive at last follow-up were considered as censored observations. Cases with missing data were excluded from the relevant analysis procedure. Minimum follow-up was 7.9 years.

Univariate analysis was performed to assess single factors using the Kaplan-Meier product limit method. The log rank test was used to determine significance of survival differences. Multivariate analyses were undertaken with the Cox proportional hazards regression model. Different combina-

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This study was supported in part by the BC Cancer Foundation.

**Acknowledgements:** The authors wish to thank Mr. R. Gallagher and Mr. J. Spinelli, Division of Epidemiology, BC Cancer Agency, Vancouver, for advice and support during the conduct and analysis of this study, and the BC Cancer Foundation and BC Cancer Agency, Victoria Clinic, for student grants.



tions of covariates were examined to determine the best prognostic model. Categories in Clark level, growth pattern, type of surgery, inflammatory reaction, surface description and primary site were coded as separate binary variables. These covariates were analyzed both as linear variables and using coded dichotomous variables.

## Results

Univariate analysis (Table 1) showed that the following factors were significant: date of diagnosis, sex, primary site including mBANS sites, growth pattern, surface description, Clark level, depth of invasion, clinical and pathological ulceration, tumor diameter and volume, lymphatic invasion, mitotic rate, inflammatory reaction, invasion to stratum corneum, pigmentation, polypoid configuration, and type of surgery. There were seven covariates in the model adopted for the basis of multivariate analysis which used coded dichotomous variables: 134 cases were uncensored. Using the logarithm of depth of invasion resulted in substantial improvement to the fit of the model.

When categorical covariates were analyzed as linear variables, significant factors were: log depth, Clark level, pathologic ulceration, primary site, type of surgery, (all  $P \leq 0.005$ ), growth pattern, mBANS sites, and lymphatic invasion. After adjusting for the effect of depth of invasion or Clark level, all the factors mentioned above remained significant. Table 2 shows the results of multivariate analyses in the present study when covariates were examined in linear fashion or as coded dichotomous variables.

There were 218 melanoma deaths and 56 deaths from other causes. Ten-

Table 1:  
Single factor analyses in clinical stage 1  
malignant melanoma

	1 <sup>a</sup>	2 <sup>a</sup>	3 <sup>a</sup>	4 <sup>a</sup>	5 <sup>a</sup>	6 <sup>10</sup>	7 <sup>a</sup>
Age	+	+	-	-	+	+	-
Sex	+	+	+	+	+	+	+
Site	+	+	+	+	-	+	+
BANS sites	-	-	NE	NE	-	NE	+
Diameter	NE	NE	NE	+	NE	+	+
Growth Pattern	+	+	-	+	+	+	+
Depth	+	+	+	+	+	+	+
Level	+	+	+	+	+	NE	+
Ulceration							
clinical	NE	+	NE	NE	NE	NE	+
pathologic	+	+	+	+	+	NE	+
Inflammatory reaction	+	NE	+	+	+	NE	+
Pigmentation	+	NE	NE	NE	-	NE	+
Mitotic rate	NE	NE	-	+	+	+	+
Lymphatic invasion	NE	NE	+	+	+	NE	+
Polypoid	NE	NE	NE	NE	+	NE	+

\* present study

NE: not evaluated

NA: not applicable

+: significant ( $P < 0.05$ )

-: not significant

Table 2:  
Recent multifactorial analyses in clinical stage 1  
malignant melanoma

	1 <sup>6</sup>	2 <sup>8</sup>	3 <sup>5</sup>	4 <sup>10</sup>	5 <sup>7</sup>	6 <sup>+</sup>	7 <sup>**</sup>
Age	+	-	-	+	+	-	-
Sex	+	+	+	+	+	-	-
Primary site	-	+	-	+	+	+	+
BANS sites	-	-	-	-	NE	-	+
Growth pattern	-	-	-	-	NE	+	+
Depth	+	+	+	+	NE	+	+
Clark level	-	-	-	-	NE	+	+
Ulceration							
clinical	+	NE	NE	NE	NE	-	-
pathologic	-	+	-	NE	NE	+	+
Mitotic rate	NE	-	-	+	NE	-	-
Epithelial cell type	-	+	-	-	NE	-	-
Lymphatic invasion	-	-	-	-	NE	+	+
ELND	+	NA	NA	NE	NE	-	-
Wide vs local excision	NE	NE	NE	NE	NE	+	+

\* present study; dichotomous variables

\*\* present study; linear variables

NE: not evaluated

NA: not applicable

+: significant ( $P < 0.05$ )

-: not significant

year disease-specific survivals for selected covariates were: 93% T1, 75% T2, 58% T3, 42% T4 primaries; Levels II 92%, III 78%, IV 58%, V 26%; primary ulceration - present 48%, absent 78%; superficial spreading 78%, nodular 52%, acral-lentiginous melanoma 43%; males 60%, females 77%; either extremity primary 77%, head and neck 63%, trunk 62%; lymphatic invasion - present 34%, absent 72%; mBANS sites - present 60%, absent 73%; local excision alone 38%, wide excision 67%, wide excision + elective lymph node dissection (ELND) 67%.

## Discussion

Analysis of survival in patients with stage 1 malignant melanoma is complex, requiring definitions of clinical and histologic features/covariates, follow-up period, and statistical methodologies. Lack of uniformity in definition of covariates may lead to difficulties in comparing results of prognostic factor analyses. For example, hands and feet may be separately coded; central pathology review rates vary; lymphocytic infiltration may be defined as two or three values; mitotic rate can be evaluated histologically and coded differently; inter-observer differences in interpretation of Clark level and Breslow depth are well known, with only 70% overall agreement among pathologists; growth pattern classification is not always possible and/or reproducible; and ELND rates and indications vary between series.

Patient selection is another factor potentially affecting survival and conclusions about the biological risks of melanoma. Referral center results are likely to be different from population-

based studies.<sup>1</sup> The BCCA, as the only provincial group offering multidisciplinary consultation for melanoma patients and providing most treatments for recurrent melanoma, is likely to have patients with poorer prognoses, and with more melanoma "events" (which may precipitate referral) after diagnosis.

Single prognostic factor results from the present study and several recent studies are summarized in Table 1.<sup>1,3-10</sup> The prognostic significance of anatomic level of invasion and depth measured by micrometer has been confirmed by all studies which assessed these factors. Other factors which were universally associated with poorer survival were: male sex, primary diameter, clinical and pathological ulceration, mitotic rate, poor inflammatory response, and lymphatic invasion. Most studies also showed age, primary site, and growth pattern to be significant.

The results of multivariate analyses in the present series showed log depth, Clark level, pathological ulceration, primary site, type of surgery, growth pattern, and lymphatic invasion to be significant irrespective of the statistical coding used. In addition, when the covariates were treated as linear variables, mBANS sites became significant. Age and sex were not significant in either model. Most previous studies have found female sex to be insignificant prognostically (Table 2).<sup>1</sup>

In 54 studies utilizing multivariate analysis, 42 showed that primary depth is the most frequently significant prognostic factor in malignant melanoma.<sup>1</sup> Five other studies of multivariate analysis of survival, not included in the review,<sup>1</sup> are summarized in Table 2. All studies, including the present, which examined depth found it to be consistently

related to survival. Primary depth is associated with several other covariates, particularly ulceration, growth pattern, cell type, mitotic activity, pigmentation, lymphocytic infiltration and primary diameter.<sup>9</sup> Depth is also largely responsible for the loss of significance of many factors when subject to multifactorial analysis.

Primary site was significant in 25 of 53 multivariate analyses of survival (Table 2).<sup>1</sup> Trunk, head and neck primaries had poorer survival in the present series; mBANS sites were significant using linear variables but not when using dichotomous variables.

Age was not a significant prognostic factor in the present and most previous multivariate analyses (Table 2).<sup>1</sup> Age is associated with depth,<sup>4</sup> the most important prognostic factor.

Superficial spreading melanoma was the most favorable growth pattern in the present study. Lentigo maligna melanoma has been reported to have a better prognosis after matching for thickness.<sup>11</sup> There were insufficient cases of lentigo maligna in the present series for survival comparison.

Primary ulceration is the remaining covariate which has frequently been positive in multifactorial analyses (Table 2).<sup>1</sup> Ulceration is mostly found in thick tumors (median thickness: 3.0 mm, compared to 1.5 mm for non-ulcerated tumors), but studies of ulceration in tumors of equivalent thickness show lower survival in ulcerated tumors.<sup>9</sup>

Patients having primary excisions <5 cm diameter had poorer prognoses in the present study. Reasons for undertaking only local excision were, however, not assessed during the chart review process. The present finding that wide excision is superior to local

excision is consistent with current melanoma surgical principles.

## Conclusion

The present study of clinical stage I malignant melanoma showed that logarithm of micrometer depth, Clark level, pathological ulceration, primary site, type of surgery, growth pattern, and lymphatic invasion were the principal prognostic factors. Modified BANS sites were only significant when linear coding was used in the multivariate analysis. □

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## \*1188

**A PHASE 1B TRIAL OF GM-CSF WITH MURINE MONOCLONAL ANTIBODY R24 IN PATIENTS WITH METASTATIC MELANOMA.** ALEFELICE, A. CHACHOUA, R. ORATZ, D. CARON, D. PEACE, L. LIEBES, HS. HOCHSTER, J. VILCEK, F. LAFLEUR, AND R. BLUM. KAPLAN COMPREHENSIVE CANCER CENTER, NYU MEDICAL CENTER, NY, NY 10016

We have initiated a phase 1b trial to test the hypothesis that GM-CSF treatment (tx) will upregulate monocyte and granulocyte antibody dependent cellular cytotoxicity (ADCC), and that the combination of GM-CSF with an antibody (R24), which mediates ADCC, leads to enhanced antitumor activity in pts with melanoma. Pt eligibility included biopsy proven melanoma,  $\leq 2$  prior chemotherapies, ECOG PS  $\leq 2$ , and adequate organ function. Clinical response and toxicity were graded using standard ECOG criteria. Monocyte and granulocyte ADCC were measured using standard chromium release assays against the SK-MEL 28 melanoma cell line. Effector/target (E/T) ratios were 32:1, 16:1, 8:1, & 4:1. GM-CSF was administered daily by sq injection for 21 days at a dose of 150  $\mu\text{g}/\text{m}^2/\text{day}$ . R24 was administered by continuous IV infusion days 8-15 at 3 dose levels: 0, 10 and 50  $\text{mg}/\text{m}^2/\text{day}$ . Each pt received only 1 tx. A total of 17 pts have been treated to date, (8m/7f; ages 37-71). R24 dose: 0 = 5 pts, 10 = 6 pts, 50 = 6 pts. All pts were evaluable for toxicity. GM-CSF toxicity included local erythema, and pruritus at the injection site. 1 pt on GM-CSF developed atrial fibrillation after 1 week of tx. Toxicity from the R24 has included gr I-II nausea/ vomiting and urticaria in all pts. 2 pts on R24 @ 10 $\text{mg}/\text{m}^2$  developed gr 3 hypertension. One of these pts developed gr 3 CHF. 1 pt on R24 @ 50  $\text{mg}/\text{m}^2$  developed grade 3 hypotension. 1 pt who had melanoma involving the GI tract developed UGI bleeding on Day 20 of tx. No objective tumor responses have been observed. 12 pts were evaluable for immunologic response. At an E/T ratio of 32:1, there was a stat sig. enhancement of monocyte ADCC after 3 weeks of tx, compared to baseline ( $p < .05$ , paired t test). There was also a modest but stat. sig. enhancement of granulocyte ADCC after 3 weeks of tx as well ( $p < .05$ ). We conclude that GM-CSF given daily sq @ 150  $\mu\text{g}/\text{m}^2$  X 21 days can enhance effector cell ADCC. Although there have been no clinical responses to date, this study is ongoing. Supported by NCI contract N01-CM-67895-01.

## \*1189

**SEQUENTIAL CHEMOTHERAPY/IMMUNOTHERAPY FOR METASTATIC MELANOMA.** J. Richards, N. Mehta, L. Schroeder, A. Dordal, Section of Hematology/Oncology, University of Chicago, Chicago, IL 60637

Seventy-four consecutive patients (pts) with metastatic melanoma have been treated with a sequence of chemotherapy and biologic agents as follows: BCNU 150  $\text{mg}/\text{m}^2$  d 1, DTIC 220  $\text{mg}/\text{m}^2$  d 1-3 and 22-25, cisplatin 25  $\text{mg}/\text{m}^2$  d 1-3 and 22-25, tamoxifen 10  $\text{mg}$  po bid x 6 wks, IL-2 1.5  $\text{mU}/\text{m}^2$  q 8hr d 4-8 and 17-21, and alfa-2a-interferon 6  $\text{mU}/\text{m}^2$  sq qd d 4-8 and 17-21. Median age of patients was 47 yrs (range: 24-73), male: female proportion was 46:28, and the median Karnofsky Performance Status was 90 (range: 70-100). Five patients had primary ocular melanoma. Sites of metastatic disease included brain (15), liver (32), lung (40), lymph nodes (39), subcutaneous sites (28) and soft tissue metastases (25). The median number of metastatic sites was 2 (range: 1-7). The three most common sites of progression were lung, brain, and liver. Forty-one of our patients were previously untreated. The response rate with this regimen was 57% with a CR = 15%, PR = 40%, MR = 3%, stable disease = 22%, and PD = 20%. Median follow-up on the study is 12.06 months. Thirty-four of sixty-eight patients have developed vitiligo-like depigmentation. Overall response rates in this group of thirty-four patients was 74%. Median time to progression on the study was 9.1 months and median survival was 14 months. Patients with no prior treatment (41) had a survival of 15.8 months compared with patients with prior treatment (33) who had survival of 10.6 months.

## 1190

**PHASE I TRIAL OF MURINE MONOCLONAL ANTIBODY MG-22 AND IL-2 IN PATIENTS WITH DISSEMINATED MELANOMA.** G.E. Goodman, I. Hellstrom, U. Stevenson, K. Steen, K.E. Hellstrom. Swedish Hospital Tumor Institute, Seattle, Washington 98104 and Bristol Myers-Squibb, Seattle, Washington 98121.

Our previous trials have documented tumor regressions in patients with disseminated melanoma after treatment with murine MAb's MG-21 and MG-22 which activate ADCC and CDC. In an attempt to augment the antitumor activity we conducted a phase I trial of MG-22 in combination with interleukin-2. Seven patients were treated with MAb MG-22 as a 7-day continuous intravenous infusion (days 8-15), at two dose levels, 75  $\text{mg}/\text{m}^2/\text{day}$  (patient 1,2) and 150  $\text{mg}/\text{m}^2/\text{day}$  (patient 3-7). The IL-2 was given as a continuous infusion on days 1-5, 8-12, 36-40, and 43-47. IL-2 dose on day 1-5 and 36-40 was fixed at  $6 \times 10^6$  IU/ $\text{m}^2/\text{day}$  and on day 49-54 at  $18 \times 10^6$  IU/ $\text{m}^2/\text{day}$ . The dose of IL-2 on days 8-12 was escalated in serial patients ( $6 \times 10^6$  IU/ $\text{m}^2/\text{day}$  patients 1,2,3,4,  $12 \times 10^6$  IU/ $\text{m}^2$  patients 5,6 and  $18 \times 10^6$  IU/ $\text{m}^2$  patient 7). Peak serum concentrations of MAb were 19  $\text{mcg}/\text{ml}$  at 75/ $\text{m}^2/\text{day}$  and 24  $\text{mcg}/\text{ml}$  at 150/ $\text{m}^2/\text{day}$ . In vivo localization of antibody to tumor was documented in all patients. All patients developed BANA, a median of 21 days after treatment. Mean NK and ADCC activity of peripheral blood mononuclear cells was augmented by IL-2 increasing from pretreatment levels of 15% and 51% to 44% and 77%, respectively. The side effects of the two agents appeared to be additive and consisted of fever, chills, nausea, vomiting, urticaria, weight gain, and azotemia. No acute antitumor activity was seen, although one patient has remained stable for >6 months.

## 1191

**ANALYSIS OF PROGNOSTIC FACTORS IN CLINICAL STAGE I CUTANEOUS MALIGNANT MELANOMA (CMM); BRITISH COLUMBIA CANCER AGENCY (BCCA) EXPERIENCE 1972 - 1981.** V. Carmichael, R.R. Davidson, K.S. Wilson. Univ. of Victoria and BCCA Melanoma Tumour Group, Victoria, B.C., Canada.

Medical records of 796 with clinical stage 1 CMM patients referred to BCCA from 1972-1981 were reviewed. Clark level 1, "borderline" melanoma pts and those lost to follow-up were excluded leaving 753 cases for analysis. The principal objective was to evaluate survival in relation to 28 clinical and pathological variables. Minimum follow-up was 7.9 yrs. BANS sites were modified (mBANS) to post. upper limb, post. trunk, neck and scalp, because of limitations of site coding. Wide primary excision was defined as > 5cm skin in re-excision specimen. Multivariate analyses were performed using Cox's proportional hazards regression model. Different combinations of covariates were examined to find the best prognostic model. When categorical covariates were analyzed as linear variables, significant factors were logarithm of primary depth, Clark level, pathological ulceration, primary site, type of initial surgery (wide vs lesser excision), growth pattern, mBANS sites and lymphatic invasion in the primary. After adjusting for effects of depth or Clark level, all the above factors remained significant. Elective regional node dissection, undertaken in 223 pts, was not a significant prognostic factor.

## 505

RANDOMIZED TRIAL OF RADIATION THERAPY (RT) PLUS DIBROMODULCITOL (DBD) VS RT PLUS BCNU IN HIGH GRADE ASTROCYTOMA. A North Central Cancer Treatment Group Study. T. Elliott, R. Dinapoli, J. O'Fallon, B. Rogers, J. Earle, R. Morton, P. Etzell, R. Marschke, B. Scheithauer. Duluth MN 55805, Rochester MN 55905, Peoria IL 61603, Des Moines IA 50265, Fargo ND 58123, Sioux Falls SD 57105.

DBD has activity in the murine ependyoblastoma model and, in humans, is converted to dianhydrogalactitol (DAG). DAG was the most active drug of 177 studied in this system (Cancer Chemother Rep 4:53) and has shown activity in patients with gliomas when used with RT initially or alone at recurrence (JAMA 241:2046). In this study 238 pts with newly diagnosed supratentorial gr. 3 or 4 astrocytoma were stratified by age, extent of resection and tumor grade. All pts received RT consisting of 4500 rad whole brain plus 1000-1500 rad to tumor volume plus 2 cm margin. By random assignment they received either concomitant DBD (200 mg/m<sup>2</sup> po x10d q5wks) or BCNU (200 mg/m<sup>2</sup> IV q7wks). Six pts (2.5%) were ineligible. Of the 232 eligible pts, 56% were male, the median age was 60, 83% had performance scores of 0-2 (ECOG), 95% had biopsy or subtotal resection, 34% were grade 3 and 60% were grade 4 (6% unknown grade). At present 71% of pts are dead, 14% are alive but off treatment, and 15% remain on treatment. Times to progression are similar for both treatment arms with medians of 22 wks. Survival curves essentially overlap with medians of 41 wks. 78% of all pts experienced leukopenia but with no meaningful difference in incidence or severity between arms. BCNU, however, produced more frequent vomiting (45% vs 15%) and also more frequent severe thrombocytopenia (< 50,000/mm<sup>3</sup>, 23% vs 14%). In comparison to the more established BCNU therapy, DBD is more favorable with regard to toxicity but currently shows no evidence of improved survival in patients with malignant glioma.

## 507

ALTERNATION VS SEQUENTIAL POLICHEMOTHERAPY (VBM) AND RADIO-THERAPY IN THE TREATMENT OF ADVANCED HEAD AND NECK CANCER. M. Merlano, M.R. Sertoli, M. Benasso, A. Grimaldi, L. Bonelli, G. Margarino, R. Corvò, E. Pallestrini, A. Barbieri, R. Rosso. Istituto Nazionale per la Ricerca sul Cancro, Genova; Istituto di Oncologia e di Radiologia, Università di Genova; \*Divisione O.R.L., Ospedale S. Martino, Genova; Servizio di Audiostimolazione, Ospedale S. Martino, Genova.

A cooperative randomized study was started in August '83 to compare in advanced Head and Neck cancer patients (pts) a sequential program of induction chemotherapy (CT) followed by locoregional treatment (radiation+surgery), Arm A, vs an alternation of 4 cycles of CT with 3 courses of radiotherapy (RT) (20 Gy in 10 days up to a total of 60 Gy), eventually followed by surgery, Arm B. The same CT was used in both Arms: Vinblastine 6 mg/m<sup>2</sup> h0; Bleomycin 30 mg h6; Methotrexate 200 mg h24-26; Cytovorum Factor 45 mg h48. The aim pursued in the first Arm is to obtain a neo-adjuvant treatment, while in the second Arm is to enhance the activity of both CT and RT through a kinetic recruitment. 69 pts entered the study, 35 in Arm A, 34 in Arm B. Median age of the whole group is 62 years, 23 pts are stage III, 46 pts are stage IV, 13 pts are female, 56 pts are male. No pts was pre-treated, median P.S., ECOG scale, is 0. The two Arms are comparable in terms of pts characteristics. The main toxicity in both Arms is represented by mucositis (14.3% vs 44%). The trial is ongoing. 46/69 pts are evaluable (20 in Arm A, 26 in Arm B). 40% CR + 15% PR and 53.8% CR + 23.1% PR have been achieved, in Arm A and B respectively. Actuarial survival is 14% in Arm A and 28% in Arm B at 26 months. No significant difference by log-rank test is yet detected in both response and survival. Grant CNR 8400803.40

## 506

ADJUVANT LEVAMISOLE IMPROVES SURVIVAL AND DISEASE-FREE SURVIVAL IN PATIENTS WITH POOR PROGNOSIS MALIGNANT MELANOMA. I. Quirt, W. Shelley, A. Bodurtha, P. McCulloch, A. McPherson, A. Paterson, R. Prentice, H. Silver, A. Willan, and K. Wilson. A Co-operative Study of the National Cancer Institute of Canada, Kingston, Ontario.

548 patients with completely resected primary melanoma, level 4, level 5, level 3 > .75 mm, satellite lesions, in-transit metastases or regional lymph node metastases were evaluated to exclude metastatic disease and randomized to 1 of 4 treatment options:

BCG (Connaught) by the multiple tine puncture disc 40 mg weekly x 5 then q 4 weeks x 3 years.

Levamisole 2.5 mg/kg p.o. on two consecutive days weekly x 3 years.

Combination - BCG alternating with Levamisole x 3 years.

Control - follow-up as in the other arms.

Median follow-up is 5.1 years. The 5 year results are:

	Total Patients	Disease-Free Survival	Survival
Control	138	.56	.63
BCG	138	.53	.61
Levamisole	135	.68	.74
Combination	137	.57	.64

Cox's proportional hazards model was used to examine the influence of treatment on outcome adjusting for stage, site, age and sex. Because 3 treatment options were compared to a single control a significance level of .0394 is required to limit the type I error to .05. With this model Levamisole was associated with a statistically significant improvement in survival (P=.036) and disease-free survival (P=.027). The values for BCG vs. control and combination vs. control were not significant.

## 508

CELLULAR LOCALIZATION OF HEPATITIS B VIRUS ANTIGENS AND IRON IN PRIMARY LIVER CANCER PATIENTS FROM SHANGHAI, CHINA. X. D. Zhou, L. DeTolla, R. P. Custer and W. T. London. Fox Chase Cancer Center, Philadelphia, PA 19111.

Surgically resected specimens were obtained from 40 patients with primary liver cancer (PLC) at Zhong Zhan Hospital, Shanghai Medical University, the People's Republic of China, between March 1983 and July 1984, consisting of tumor and adjacent uninvolved liver tissue. Localization of hepatitis B surface and core antigens (HBsAg, HBcAg) and iron in hepatic parenchymal and tumor cells was determined by peroxidase-antiperoxidase and Perl's Prussian blue methods. Of the 40 tumors, 39 (97.5%) were primary hepatocellular carcinomas (PHC) and one PHC mixed with cholangiocarcinoma. The serum HBsAg positive rate was 80.0% (32/40). Cirrhosis was observed in 90.0% (36/40). HBsAg was identified in uninvolved liver in 82.5% (33/40), in tumors 35.0% (14/40). HBcAg was detected in liver in 25.0% (10/40), but in only 7.5% (3/40) of the tumors. Stainable iron was found in 65.0% (26/40) of livers and 10.0% (4/40) of tumors. Twenty-two of 33 PLC patients (66.7%) with HBsAg positive cells in their livers also showed stainable iron, compared with 4 of 8 HBsAg negative cases, suggesting that hepatocytes with higher intracellular iron are more likely to be infected with hepatitis B virus (HBV). The high prevalence of HBsAg and cirrhosis in PHC indicates that HBV plays an important etiologic role of hepatocarcinogenesis in China. However, there were 8 serum HBsAg negative (20.0%) and 5 noncirrhotic (12.5%) PHC cases in our series, the etiology of which remains questionable.

(Supported by the Cancer Research Institute, Inc., New York, NY.)

# Improved Survival in Patients With Poor-Prognosis Malignant Melanoma Treated With Adjuvant Levamisole: A Phase III Study by the National Cancer Institute of Canada Clinical Trials Group

By Ian C. Quirt, Wendy E. Shelley, Joseph L. Pater, Audley J. Bodurtha, Peter B. McCulloch, Thomas A. McPherson, Alexander H.G. Paterson, Robert Prentice, Hulbert K.B. Silver, Andrew R. Willan, Kenneth Wilson, and Benny Zee

Five hundred forty-three patients with completely resected malignant melanoma who were considered to have a significant risk of developing recurrent disease were randomized to one of four study groups. One group received levamisole 2.5 mg/kg on 2 consecutive days weekly for 3 years, a second group received bacillus Calmette-Guérin (BCG) for 3 years. A third group alternated 8-week courses of BCG and levamisole for 3 years and a fourth group underwent clinical assessment at the same frequency as the three treatment groups. The median duration of follow-up is 8.5 years. The percentage of reduction in the death rate and the recurrence rate in the treatment groups compared with the control group was calculated using the Cox proportional hazards model and adjusted for age, sex, and stage as covariants. The patients treated with levamisole were estimated to have a 29% reduction in

both the death rate ( $P = .08$ ) and the recurrence rate ( $P = .09$ ) compared with patients receiving no further treatment. Fifty-five patients discontinued levamisole early because of gastrointestinal intolerance or arthralgia, myalgia, fever, and immune leukopenia. The patients treated with BCG alternating with levamisole experienced a 10% reduction in the death rate and a 6% reduction in the recurrence rate, and the patients treated with BCG alone experienced a 4% reduction in the death rate and a 3% increase in the recurrence rate compared with the control group. The degree of improvement experienced by the patients that were treated by levamisole is of sufficient magnitude to warrant further investigation of this dose of levamisole as adjuvant treatment in patients with melanoma. *J Clin Oncol* 9:729-735. © 1991 by American Society of Clinical Oncology.

LEVAMISOLE was synthesized in 1966 and became available as an anthelmintic for human use in 1968. In 1971, Renoux and Renoux<sup>1</sup> observed an increased immunity against *Brucella* infection in *Brucella*-vaccinated mice after levamisole medication. Additional studies indicated that levamisole could restore several T-cell functions and restore the phagocyte function of polymorphonuclear cells, monocytes, and macrophages. The most pronounced effects were to restore subnormal T-lymphocyte or phagocyte functions. Normal immune functions usually could not be augmented.<sup>2</sup>

In 1973, Tripodi et al<sup>3</sup> demonstrated that levamisole could restore skin test reactivity to dinitrochlorobenzene in anergic patients with underlying cancer. In 1980, Spittler and Sagebiel<sup>4</sup> reported the results of a randomized trial of adjuvant levamisole in a fixed dose of 150 mg orally on 3 consecutive days every 2 weeks in patients with completely resected poor-prognosis melanoma. In their patients with primary melanoma, they observed a

trend to improved overall survival with a two-sided  $P$  value of .07 and concluded that an additional study was warranted.

In Canada in the mid-1970s, bacillus Calmette-Guérin (BCG) was in wide use as an immunostimulant in patients with melanoma, but no randomized study had proved its value.

It was concluded that a large prospectively randomized study of adjuvant BCG and adjuvant levamisole was warranted.

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From The Princess Margaret Hospital, Toronto; National Cancer Institute of Cancer Clinical Trials Group, Kingston; and Queen's University, Kingston; Ontario Cancer Foundation-Hamilton Regional Centre, Hamilton; Dalhousie University, Halifax; Cancer Control Agency of British Columbia, Vancouver; and Cross Cancer Institute, Edmonton, Canada.

Submitted April 5, 1989; accepted October 18, 1990.

Supported by the National Cancer Institute of Canada.

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0732-183X/91/0904-0020\$3.00/0



## METHODS

### Eligible Patients

To be eligible for this study patients must have had either a primary melanoma that was level 4, level 5, or level 3 greater than 0.75 mm in vertical height; or any level with satellite lesions within 3 cm of the primary melanoma; or any level with in-transit metastases or regional lymph node involvement with melanoma. Patients with completely excised lymph node involvement from melanoma but no known primary lesion and patients with completely excised recurrent melanoma that was isolated to the regional lymph node area draining the previous primary were also eligible for the study. Pathology review was conducted by a local reference pathologist in each participating center to determine initial eligibility, and then the slides of all patients with primary melanoma were reviewed by one central pathologist. After complete surgical excision, staging procedures were performed to ensure that patients were free of detectable residual disease. Patients had to be between 16 and 70 years of age, could not have a previous history of another malignancy or rheumatoid arthritis, could not be on continuous corticosteroid therapy, and had to be entered on the study within 12 weeks of surgical excision.

### Randomization and Treatment Schedules

After eligibility had been established, the patients were approached about entry into the study. The complete structure of the study, including the toxicities of the proposed treatments, was explained to the patients, and written informed consent was obtained. The patients were then randomized to one of four groups. One group received 40 mg of the Connaught strain of BCG by the multiple-time puncture disk weekly for 4 weeks then once every 4 weeks to complete 3 years of treatment. The BCG was administered on the upper outer aspect of each extremity in rotation. A second group of patients received levamisole 2.5 mg/kg orally on 2 consecutive nights weekly for 3 years. A third group received the same schedule of BCG as the BCG group for an 8-week period of time, then received levamisole for an 8-week period of time, and finally, alternated 8-week courses of BCG given twice in the 8-week period, with levamisole weekly for an 8-week period to complete 3 years of treatment. Because of this alternating sequence, the overall dose of either BCG or levamisole per unit time would be 50% when compared with the BCG-alone arm or the levamisole-alone arm. A fourth group of patients underwent careful observation at the same frequency as the three treatment groups.

At entry onto the study, a full history was taken, a full physical examination was performed, and a complete blood count, BUN, creatinine, bilirubin, alkaline phosphatase, SGOT (AST), protein electrophoresis, urinalysis, chest x-ray, and 10 tuberculin unit (TU) purified protein derivative (PPD) skin test were obtained. For the first 3 years after a patient was enrolled on the study, a history, physical examination, complete blood count, liver function profile, protein electrophoresis, and PPD skin test was obtained every 3 months and a creatinine, urinalysis, and chest x-ray was obtained every 6 months. After 3 years from entry on

the study, the clinical assessment and laboratory tests were obtained every 6 months, and after 5 years from enrollment on the study, these evaluations were performed at yearly intervals.

Patients were free to withdraw from treatment at any time after enrollment on the study.

Any investigational treatment was discontinued if the patient experienced a recurrence of their melanoma.

### Statistical Analysis

In advance of the study, it was determined that to detect a 20% improvement in 5-year survival with a significance level of .05 and a power of .9, we would require 130 patients in each treatment arm.

The study was analyzed by the intention to treat. Therefore, all patients allocated to a treatment group were analyzed as part of that group even if they discontinued treatment early because of side effects or refused to take the treatment after having given informed consent. The relapse-free survival and overall survival curves, calculated using the Kaplan-Meier method, are plotted from the date of entry on to the study. For relapse-free survival curves, patients who died of other causes were censored at the time of death; however, on the overall survival curves, all deaths were counted as failures.

The percentage of reduction in death rates and recurrence rates were calculated through the Cox proportional hazards model. We estimated the parameters in the Cox proportional hazards model by maximization of the partial-likelihood function. The death rates and recurrence rates for each treatment were then calculated by substituting the corresponding mean covariate vectors into the Cox proportional hazards model. Using these estimates, we obtained the percentage of reduction in death rate and recurrence rates for each study treatment relative to that of the control. The results for unadjusted analyses were calculated from the simplest Cox model, which include only the treatment effect. The results for the adjusted analyses include age, sex, and stage as covariates.

The proportional hazards model was also used to determine the statistical significance of the effect of treatment and prognostic factors on disease-free survival and overall survival. For the analysis, stage was divided into (1) primary only, (2) primary with regional (satellite, in transit, or nodal spread), and (3) nodal presentation or recurrence. Primary-only cases were further subdivided according to depth of invasion into three categories (.76 to 1.49 mm; 1.5 to 4 mm; and > 4 mm). Level was examined as a categorical variable and age as a continuous variable. Each of the three treatment arms was compared with the single control arm. Since there was no prespecified hypothesis as to which arm would be superior, the conventionally calculated *P* values presented in the following sections underestimate the probability that the observed results are due to chance. Two-sided *P* values adjusted for the other factors in the model are quoted for all treatment comparisons and prognostic factors.

The product-limit estimate of the proportion of patients free of relapse or alive at 5 years for each of the three treatment arms was compared with that of the control using Greenwood's formula.<sup>5</sup>

## RESULTS

Between February 1978 and December 1982, 577 patients were randomized. Of these, 34 were subsequently found to be ineligible. On central pathology review, 12 patients did not have melanoma; 16 patients had melanoma that was too superficial to meet the eligibility requirements; one patient had received previous chemotherapy; one patient had a conjunctival rather than cutaneous melanoma, and the depth of invasion could not be assessed; one patient was not under the care of a participating physician; one patient had metastatic disease at initial assessment; one patient had a concurrent lymphoma; and one patient was older than 70 years of age. Fortunately, the number of ineligible patients was the same in all four groups. Therefore, 543 eligible patients are available for evaluation. The median duration of follow-up on the study is 8.5 years. The pretreatment characteristics of the patients are summarized in Table 1.

The relapse-free survival experienced by the four groups of patients is shown in Fig 1. Compared with the control group, the group of patients who received adjuvant levamisole experienced a 29% reduction in the adjusted risk of recurrence, the group receiving BCG alternating with levami-

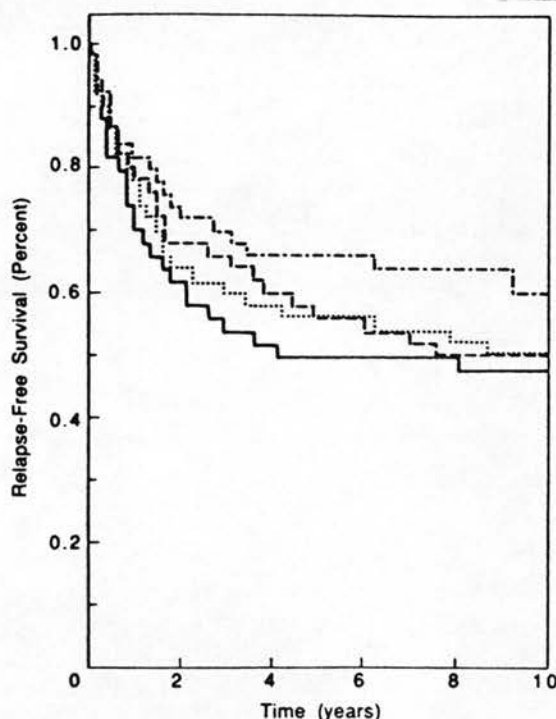


Fig 1. Relapse-free survival curves for patients receiving (---) levamisole, (—) BCG, (.....) a combination of BCG alternating with levamisole, and (- · - · -) the control group.

sole had a 6% reduction in the adjusted risk of recurrence, and the group receiving BCG alone experienced a 3% increase in the adjusted risk of recurrence.

The overall survival curves for the four treatment arms are shown in Fig 2. Compared with the control group, the levamisole group experienced a 29% reduction in the adjusted risk of death, the group receiving BCG alternating with levamisole had a 10% reduction in the adjusted risk of death, and the group receiving BCG alone experienced a 4% reduction in the adjusted risk of dying.

The product-limit estimates of 5-year relapse-free survival and overall survival percentages are summarized in Table 2.

The assessment of the statistical significance of our results depends on the end point chosen. The original sample-size calculation was based on the assumption that the major point of interest was the long-term (5-year) proportion of patients alive and free of disease. Two-sided *P* values using Greenwood's formula to assess the statistical significance of the differences in the proportions observed in this trial are presented in Table 3.

An alternative approach to the analysis of such

Table 1. Pretreatment Characteristics

	Control No.	BCG No.	Levamisole No.	Combination No.
<b>Sex</b>				
Female	63	54	68	55
Male	74	82	67	80
<b>Stage</b>				
Primary	103	94	99	98
Satellitosis	3	2	2	4
In-transit	1	2	0	4
Node-positive	30	38	34	29
Mean age (years)	47.7	48.7	44.8	46.1
<b>Site of primary (primary patients only)</b>				
Head and neck	12	12	9	9
Lower limb	28	22	26	23
Trunk	47	43	43	44
Upper limb	16	17	21	22
<b>Depth of primary (primary patients only)</b>				
Unknown	1	0	1	0
0.76-1.5	39	32	38	43
1.51-2.5	31	28	33	22
2.51-4.0	17	19	15	18
> 4.0	15	15	12	15
<b>Total patient</b>	<b>137</b>	<b>136</b>	<b>135</b>	<b>135</b>

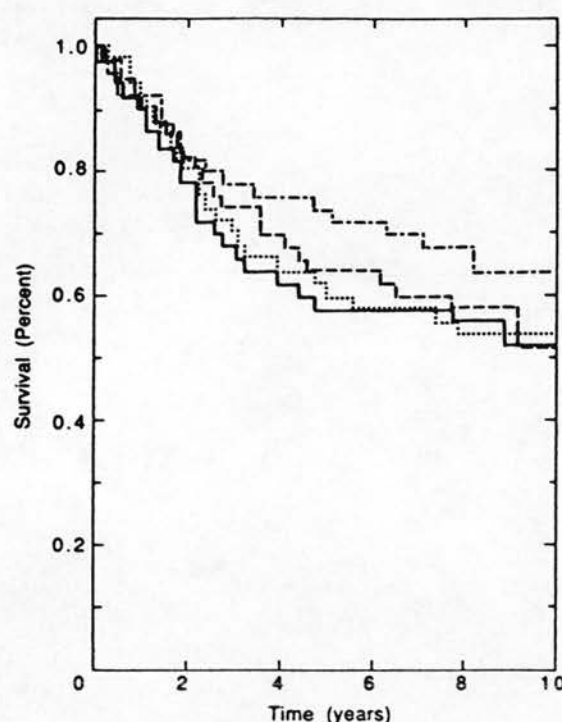


Fig 2. Overall survival curves for patients receiving (---) levamisole, (—) BCG, (.....) a combination of BCG alternating with levamisole, and (— · —) the control group.

data is to consider prolongation of survival or disease-free survival rather than point in time "cure" rates as the end point of interest and to use time-to-event methods in the analysis. The two-sided *P* values generated by applying Cox's model to our data are summarized in Table 4.

To determine if levamisole was particularly effective or ineffective in any subgroup of patients, a separate multifactor analysis of overall survival with prognostic factor/treatment interaction terms in the model was performed only on the patients in the control and levamisole arms. The interactions examined were treatment/age, treatment/stage, and treatment/sex. The *P* values for these interactions in the multifactor model were: .17 for treat-

Table 2. Product-Limit Estimates of 5-Year Relapse-Free Survival and Overall Survival Percentages

	5-Year Relapse-Free Survival	5-Year Overall Survival
Control	55	62
Levamisole	66	74
Levamisole alternating with BCG	58	65
BCG	50	59

Table 3. *P* Values for 5-Year Proportions

	Relapse-Free Survival	Overall Survival
Levamisole v control	.0672	.0268
Levamisole alternating with BCG v control	.7493	.6329
BCG v control	.3987	.6226

ment/age, .45 for treatment/stage, and .43 for treatment/sex.

Because the time interval from definitive treatment to entry on the study was quite long, a separate analysis was performed to determine if patients entered on the study within 6 weeks of surgery had different survival experiences from those entered after 6 weeks. No such difference was observed.

The study included a broad base of patients ranging from low-risk primary melanoma to high-risk patients with regional lymph node metastases from melanoma. The same degree of proportional improvement in relapse-free survival and overall survival was observed in patients with primary melanomas less than 1 mm in vertical height, patients with intermediate-thickness melanomas (1 mm to 4 mm), and patients with high-risk melanoma (primary melanoma > 4 mm, in-transit metastases from melanoma, and lymph node metastases from melanoma).

No treatment-related deaths were observed in this study. Eighteen deaths that were not related to melanoma were documented; six in the control arm, six in the BCG arm, three in the levamisole arm, and three in the BCG alternating with levamisole arm.

The analysis of prognostic factors by the proportional hazards model confirmed that stage, sex, and age were significant prognostic factors.

The group that received BCG experienced local inflammatory reactions at the vaccination sites and occasional mild fever the day following the injection but otherwise had no ill effect. The toxicity from levamisole is summarized in Table 5. In the arm that alternated BCG with levamisole, it was not possible to attribute side effects specifically to

Table 4. Cox Proportional Hazards Model Adjusted for Sex, Age, and Stage

	Relapse-Free Survival	Overall Survival
Levamisole v control	.0800	.0964
Levamisole alternating with BCG v control	.7280	.5926
BCG v control	.8707	.8053



Table 5. Levamisole Toxicity

Side Effect	No.
Nausea	33
Vomiting	8
Anorexia	2
Bitter taste	14
Leukopenia	14
Fever	11
Arthralgia/myalgia	11
Skin rash	5
Mouth ulcers	2
None	64
Total patients	135

either the BCG or the levamisole; therefore, the levamisole toxicity is presented for the 135 patients who received levamisole alone. Two constellations of side effects were seen. One group of patients experienced a bitter metallic taste that led to anorexia, nausea, and, in some patients, vomiting. A second group of patients experienced fever, arthralgia, and myalgia. Skin rash and mouth ulcers were less frequent. Fourteen patients developed an absolute neutrophil count below 2,000/mm<sup>3</sup>. In all cases the WBC count normalized rapidly when levamisole was discontinued, and no evidence of infection was seen in any patient while the blood count was reduced. Fifty-five patients discontinued levamisole early because of toxicity. Nineteen patients received levamisole for 1 to 3 months, 18 patients received it for 4 to 12 months, 11 patients received it for 13 to 24 months, and seven patients received it for 25 to 35 months. Forty-seven patients were able to complete a full 3 years of treatment. The other patients had levamisole discontinued early because of relapse.

### DISCUSSION

The concept of attempting to improve the prognosis of patients with melanoma by stimulating the immune system is not new. It has long been recognized that patients with primary melanoma can experience immune destruction of portions of their primary melanoma and that patients with widely metastatic melanoma can experience complete disappearance of all metastatic disease without specific treatment. Over the last 2 decades, many attempts have been made to treat metastases from melanoma and to prevent recurrence of melanoma by using either specific killed-melanoma-cell vaccines or nonspecific bacterial

and viral vaccines. Unfortunately, none of these treatment modalities has proved effective.

Spitler and Sagebiel<sup>4</sup> reported the results of their randomized trial of levamisole versus placebo in patients with poor-prognosis malignant melanoma. They used a standard dose of 150 mg for 3 consecutive days every 2 weeks. They did observe a trend to improved overall survival in patients with primary melanoma with a two-sided *P* value of .07.

Loutfi et al<sup>6</sup> published the results of another trial of levamisole versus placebo in 156 patients with level 3, 4, and 5 melanoma. The dose of levamisole was 150 mg twice a week for 3 years. Both the disease-free survival and overall survival were slightly better in the placebo group. The authors state that with 73 patients in the levamisole group and 64 patients in the placebo group, their numbers were too small to state definitively that no difference existed. They did conclude that levamisole is unlikely to reduce the risk of dying below 60% of what it would be with no treatment. In our study we observed a 29% reduction in the risk of dying in the levamisole group compared with the no treatment group.

Lejeune et al<sup>7</sup> issued the first report of an ongoing study that randomized patients who had primary melanoma, with level 3 with a thickness equal or exceeding 1.5 mm, level 4, and level 5 to dacarbazine, levamisole, or placebo. The levamisole was taken on 2 consecutive days every week for 2 years. The daily dose of levamisole was 150 mg for patients up to and including 70 kg, 200 mg for patients 71 to 90 kg, and 250 mg for patients above 90 kg. All patients with extremity melanoma underwent lymph node dissection, and patients with lymph node metastases were not eligible for the study. The mean follow-up time was 3 years. No reduction in either disease-free survival or overall survival was observed in the 101 patients in the levamisole arm compared with the 96 patients in the control arm. Patients with extremity melanoma underwent prophylactic lymph node dissections. Because the patients with extremity melanoma and occult lymph node metastases were eliminated from the trial, it is likely that patients on this study had a significantly reduced chance of experiencing recurrence than did the patients on our study.

Amery<sup>8</sup> published the results of a placebo-controlled trial of levamisole in resectable bron-

chogenic carcinoma. A standard dose of levamisole 150 mg/d for 3 days every 2 weeks was administered. A subsequent analysis of these results pointed out that most of the benefit had been achieved in patients less than 70 kg in weight and it was recommended that a minimum dose of 2.5 mg/kg of levamisole should be used in future studies.<sup>9</sup> This same conclusion was reached by Van Eygen et al<sup>10</sup> in the treatment of upper respiratory tract infections in children. Because of these observations, we used a levamisole dose of 2.5 mg/kg on 2 consecutive nights each week.

The dose intensity of levamisole was appreciably higher in our study than in those reported by Spitler and Sagebiel<sup>4</sup> or Loutfi et al.<sup>6</sup> Over a 2-week period of time, an 80 kg patient received 800 mg of levamisole in our study compared with 450 mg in the study by Spitler and Sagebiel and 600 mg in the study reported by Loutfi et al.

Our patients who received levamisole experienced an improvement in both relapse-free survival and overall survival. The degree of improvement is of sufficient magnitude to warrant further investigation of levamisole in patients with melanoma. However, these results highlight the importance of the choice of end point in interpreting the results of clinical trials. If one's interpretation is based on the originally chosen end point for the study, 5-year survival, the results observed in favor of levamisole reach conventional levels of significance. On the other hand, comparisons based on the entire disease-free or overall survival experiences of the groups indicate a moderate, but not quite statistically significant, benefit for levamisole. Which of these end points is more appropriate in these circumstances is debatable, but a case can be made for considering the status of the patients at a later point in time most relevant. A treatment that has the ability to kill a small number of residual tumor cells would only be anticipated to be of benefit to individuals with a very small burden of residual disease. One would not anticipate that these patients would experience a relapse in the first several months after they had entered a clinical trial. Therefore, it is not surprising that the relapse-free survival and overall survival curves separate only after a 2- to 3-year interval. The fact that the survival curves stay together for this period of time when large numbers of patients are represented on the curves

tends to minimize differences when the Cox proportional hazards model is used.

It is difficult to draw conclusions from the relapse-free survival and overall survival curves experienced by the group that received BCG alternating with levamisole. When the study was formulated we were concerned that excessive toxicity might be seen if the two treatments were administered concurrently. Therefore, patients were treated with BCG initially for an 8-week period of time and then were given levamisole for an 8-week period of time, followed by alternating 8-week courses of BCG and levamisole. Hence, the patients in the combination group all had an 8-week delay before receiving levamisole and only received 50% of the dose of levamisole that patients in the group that received levamisole alone were treated with. Some patients relapsed during the initial 8 weeks that they received BCG without ever receiving levamisole.

Other investigators have reported that adjuvant levamisole or adjuvant levamisole combined with chemotherapy could reduce recurrence rates and improve survival in other solid tumors. The Study Group for Bronchogenic Carcinoma<sup>9</sup> performed a double-blind control trial of levamisole in patients with completely resected bronchogenic carcinoma. They observed 20 recurrences and 12 deaths in the 60 patients who were treated with placebo and 10 recurrences and seven deaths in the 51 patients who were treated with levamisole 150 mg orally on 3 consecutive days every 2 weeks. Laurie et al<sup>11</sup> compared both levamisole alone and levamisole combined with fluorouracil (5FU) to an observation alone in patients with Dukes' B and Dukes' C colorectal cancer. In this study, a significant reduction in recurrence rates and improvement in survival was observed in the group of patients that received the combination of 5FU and levamisole. The group of patients that received levamisole without 5FU also experienced a reduced recurrence rate and improved survival but the difference was less statistically significant than observed with a combination of 5FU and levamisole. The major benefit was experienced by patients with Dukes' C rather than Dukes' B colon cancer. Moertel et al<sup>12</sup> then conducted a larger confirmatory study of 5FU combined with levamisole and levamisole alone compared with observation in patients with Dukes' B and Dukes' C colorectal cancer. The preliminary analysis of their results

indicates a highly statistically significant improvement in relapse-free survival and an improvement in overall survival in the patients who were treated with 5FU combined with levamisole. At the time of reporting, no improvement had been observed in patients treated with levamisole alone. This raises the possibility that the levamisole may be acting by modifying the metabolism of 5FU and making it more effective as an adjuvant treatment rather than having any immune modulating effect.

We did observe significant gastrointestinal toxicity, arthralgia, myalgia, fever, and immune neutropenia. Levamisole has produced fatal immune neutropenia in patients with rheumatoid arthritis; therefore, patients with rheumatoid arthritis should not be treated with levamisole, and patients who receive levamisole should have their WBC count followed frequently.

The degree of improvement is of sufficient magnitude to warrant further investigation of levamisole in patients with melanoma, particularly in view of the recent reports that the use of this medication contributes to prolongation of survival in the adjuvant therapy of patients with colorectal carcinoma.<sup>11,12</sup> Our results are only marginally significant but are of a sufficient magnitude to be clinically relevant if they are confirmed in future clinical trials. Future studies should concentrate on defining more accurately the mechanism by

which levamisole stimulates immunity and on determining the ideal dose to achieve immune stimulation. Such studies might identify subgroups of patients that could be benefited by adjuvant levamisole and might suggest novel combinations of other biologic response modifiers with levamisole to be studied in the future.

# ACKNOWLEDGMENT

We are grateful to Cathy Bedlington for her assistance in the preparation of this manuscript. We thank Janssen Pharmaceutica Incorporated (Canada) for supplying the levamisole and Connaught Laboratories for supplying the BCG. We are grateful to Dr Peter Mansell for his initial work in coordinating the study and to the following investigators who contributed patients to the study: Drs P. Dent, A. Kibrite, L. Dionne, A. Desgagnés, G. Boileau, D. Thompson, D. Klaassen, C. Cripps, W. Hirte, J. Maroun, V. Young, E. Rapp, R. Taylor, D. Stewart, W.K. Evans, M. Blackstein, R. Nimmagadda, N. Grant, L. Deschenes, P. Galbraith, J. Pater, A. Ginsburg, C. Tanser, A. Figueredo, A. Seidenfeld, D. Osoba, J. Rusthoven, K. Pritchard, B. Dingle, H. Kreiger, G. Kutas, H. Abu-Zahra, J. Duffin, T.W. Wilson, A. Aleem, B. Malik, A. Naidoo, M. Baker, D. Sutton, D. White, H. Bush, D. Walde, W. Beecroft, J. Lezack, M. Levitt, B. Weinerman, P. Galbraith, J. Beatty, D. Bowman, L. Jerry, N. Murray, and P. Klimo. We also thank the following local reference pathologists: Drs G.M. Fraser, S.U. Khaliq, M. Plante, R. Fortin, S. Jacob, W. Duguid, E. Liepa, J. Roberts, Y. Bedard, L. From, M. Smout, V. Baryluk, G. Wenckenbach, G. Hogg, G. Cates, F. Alexander, D. Willans, and A. Worth.

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Phase II Study of Mitolactol in Advanced Malignant Melanoma<sup>1,2</sup>Nevin Murray,\* Hulbert Silver, Amil Shah, and Kenneth Wilson<sup>3,4</sup>

Metastatic malignant melanoma is notoriously resistant to chemotherapy, particularly after previous drug treatment. Mitolactol has been reported to produce response rates up to 30% (1,2). One of these studies reported responses to mitolactol in patients previously treated with dacarbazine and a nitrosourea (2). Subsequent trials of either mitolactol alone, using slightly differing doses and schedules (3,4), or mitolactol and semustine (5) did not achieve such encouraging results. We report our experience with an intermittent oral regimen for previously treated patients with advanced malignant melanoma.

All patients had biopsy-proven metastatic melanoma with measurable disease in an unirradiated area. Mitolactol was offered as a second-line chemotherapy when dacarbazine or a nitrosourea had failed. Mitolactol, at a dose of 180/mg/m<sup>2</sup>/day  $\times$  10 days, was given orally at 28-day intervals. The dose was escalated by 10% in subsequent cycles in the absence of significant side effects.

The characteristics of 21 patients with metastatic melanoma treated on this study are shown in table 1. Nineteen patients developed progressive disease within 2 months. Two patients, one with lung metastasis and another with subcutaneous lesions, had stable disease. However, a careful review of the pretreatment growth rate of these indolent melanomas indicated no change in the doubling time related to drug treatment.

The median survival time of the entire group was 5 months. The median survival time for patients with progressive disease was 4 months; for stable disease patients, it was 14 months. The long survival of the two stable disease patients was probably due to their slow-growing tumor rather than a treatment benefit.

In conclusion, although mitolactol can be given safely with this dose schedule, we found the response rate of the drug in patients with previously treated metastatic melanoma to be < 15% (rejection error < 5%). This may be due to cross-resistance with other alkylating agents or it

TABLE 1.—Patient characteristics

Characteristic	No. of Patients (%)
Evaluable	21
Median age in yrs (range): 57 (34-70)	
Sex	
Male	8
Female	13
Performance status*	
0-1	15 (71)
2-3	6 (29)
Sites of disease	
Soft tissue	8 (38)
Lung	7 (34)
Liver	3 (14)
Abdomen (excluding liver)	3 (14)
Prior chemotherapy	
Dacarbazine	18 (85)
Lomustine	2 (10)
None	1 (5)
Prior radiotherapy	5
No. of cycles of mitolactol	
1-2	19
4-10	2
Toxicity	
Nausea and vomiting	3 (14)
Leukopenia (wbc count < 3000/mm <sup>3</sup> )	7 (33)
Thrombocytopenia (platelet count < 100,000/mm <sup>3</sup> )	4 (19)
Infection	0
Bleeding	0
Response rates	
Partial response (> 50% tumor area reduction)	0
Stable disease (< 50% tumor area reduction)	2
Disease progression (> 25% tumor area increase)	19

\* Eastern Cooperative Oncology Group criteria.

may merely indicate lack of activity of this drug. Further studies of this schedule of mitolactol for patients previ-

<sup>1</sup>Received Aug 21, 1984; revised Dec 10, 1984; accepted Dec 17, 1984.

<sup>2</sup>Mitolactol was supplied by the National Cancer Institute, Bethesda, MD.

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<sup>4</sup>We thank Lorraine Cho for secretarial assistance and Linda Garant for chart reviews.

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ously treated with chemotherapy for advanced malignant melanoma are not recommended.

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